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A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE

A collection of papers comprising two symposia of one day each presented before the Divisions of Chemical Literature and Medicinal Chemistry at the 124th and 126th national meetings of the American Chemical Society, Chicago, September 1953 and September 1954.

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The Literature of Analgesics

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Relief of pain has been one of the oldest and most widely studied problems of medical art and related sciences—pertinent documentation is found even in papyri of the ancients. The historical development of the literature of analgesics is set forth; specialized analgesic literature and a number of the more important, recent reviews on the subject are mentioned. Some recent advances are briefly reviewed with special emphasis given to the chemical aspects, to the bioaction, and in some cases, to the clinical experiences made with selected drugs.

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In modern times new anesthetic agents, analgesics, hypnotics, nerve sections, and laboratory studies on the physiology and psychology of pain have gone a long way toward making the relief of pain a widely studied and thoroughly investigated scientific problem.

The word "analgesia" entered the medical, chemical, and related literature with the discovery and isolation of morphine by Sertürner in 1803 *(63, 64)*. It is by definition the absence of sensibility to pain which is physiologically due to a raising of the pain threshold. Anesthesia—pain relief by loss of feeling—was introduced into the medical literature with the discovery of ether by Sir Humphrey Davy, C. W. Long, Wm. Morton *(35)*, and others *(8, 35)*, in the early part of the 19th century.

The use of cocaine by the Viennese opthalmologist, Köller, in 1884, opened new vistas in the field of pain relief *(46–48)*. Since then the synthesis pharmacology, and clinical use of local anesthetics have occupied a large portion of the literature.

The Oldest Literature of Pain Relief

The Old Testament (*52*) and the Talmud contain reference to the ancient practice of inducing sleep by artificial means when otherwise sleep would not come because of pain. In Homer's Odyssey (9th century, B.C.) we find that Helen of Troy put some drug into wine to "lull all pains and anger and bring forgetfulness to every sorrow" (*35, 41*). This is certainly one of the oldest references to the use of an analgesic, although its nature is not known. Perhaps it was opium. The collection of opium itself was first described by Diagoras of Melos around 380 B.C. and by Theophrastus about the third century, B.C. Herodotus, a Greek historian, knew about a Scythian custom "of inhaling the fumes of hemp" to overcome pain and induce sleep, another example of a very old use of a narcotic—Indian hemp, now known as hashish, is illegally used as a smoke for its intoxicating effects. Dioscorides, a physician in Greece who lived in the middle of the first century, mentions the use of mandragora, an herb of the nightshade family, as a pain-killing agent; the root of the plant was boiled in wine and administered prior to surgical operations (*15, 35*).

One of the first references to analgesic pills was made by Celsus during the first century, A.D., in his "De Medicina" (*13, 55, 66*). In the literature of medieval times, the term "laudanum" is ascribed to the physician and alchemist Paracelsus (1493-1541). An oil for surgical anesthesia was described by Hugo de Lucca as early as the 13th century. It contained opium, the juices of Hyoscyamus, hemlock, and mandragora. Giambattista Porta, a surgeon of Naples, used an essence made of Hyoscyamus, nightshade, poppy, and belladonna *(37)*.

Shakespeare, who was familiar with the narcotic effects of various drugs, in "Cymbeline" makes the court physician, Cornelius, prescribe a drug which:

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Will stupefy and dull the sense awhile, but there is
No danger in what show of death it makes,
More than the locking up the spirits a time,
To be more fresh, reviving. *(65)*

At present the literature of pain relief, under its various headings, has grown tremendously (Tables I and II). In fact, information on these subjects is not limited to a specialized literature of pain relief (except for limited numbers of more recent publications dealing exclusively with this problem) but one may say that the literature of analgesics is now part of the chemical, physiological, pharmacological, and clinical literature, and chemists who want to obtain information on analgesics must use the same methods that have to be applied in other literature searches.

Table I. Modern Journals Devoted to Problems of Anesthesia and Analgesia

Name of Journal	*Society, Author, Publisher*	*Published*
Anesthesiology	The American Society of Anesthesiologists	Bimonthly
Anaesthesia	Association of Anaesthetists of Great Britain and Ireland	Quarterly
Anesthésie et analgésie	Société Francaise d'Anesthésie et d'Analgésie	
Acta Anaesthesiologica Belgica	Société Belge de Chirurgie, Bruxelles (part of Acta Chirurgica Belgica)	
British Journal of Anaesthesia	John Sherratt & Son, Altrincham, England	Quarterly
Current Researches in Anesthesia and Analgesia	International Anesthesia Research Society ..	Bimonthly
Der Anaesthesist	Österreichische Gesellschaft für Anaesthesiologie, Vienna; Springer Verlag, Berlin	Bimonthly
Minerva Anestesiologica	Società Italiana di Anestesiologica	
Revista argentina de anestesia y analgesia	Asociación Argentina de Anestesia, Buenos Aires	3 times a year
Revista brasileira de anestesiologia		Quarterly
Schmerz Narkose-Anaesthesie	Georg Thieme, Leipzig	Apparently discontinued in 1944

Table II. Abstracts, Special Texts, and Review Articles[a]

Name	*Society, Publisher*
Anesthesia Abstracts	Burgers Publishing Co., Minneapolis
Chemical Abstracts	AMERICAN CHEMICAL SOCIETY
Chemisches Zentralblatt	Akademie-Verlag G.m.b.H.
Biological Abstracts	
Excerpta Medica	Williams & Wilkins Co.
Current List of Medical Literature	Armed Forces Medical Library
Quarterly Cumulative Index Medicus	American Medical Association
Quarterly Reviews	Chemical Society, London, 1948, 1951
Annals of the New York Academy of Sciences Vol. 51: "Newer Synthetic Analgesics"	lished November 1948. New York Academy of Sciences, Conference on Newer Synthetic Analgesics, May 1948 pub-
United Nations Bulletin of Narcotics	

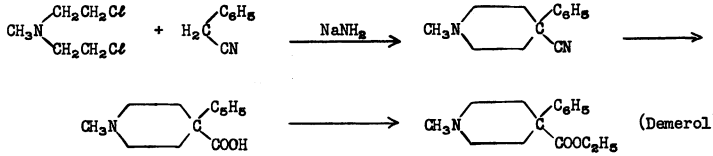
[a] Also see *(6, 36, 39, 40, 49, 50, 57)* for additional review articles.

Some Recent Developments Revealed in the Literature of Analgesics

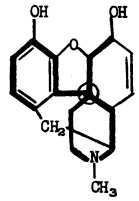
In the field of synthetic analgesics, the prime requirement has always been to find potent, nonhabit-forming drugs of low toxicity. This task has fallen short of the goal, but it has made significant advances.

With the possible exception of the salicylates, antipyrine, pyramidon, and aspirin, all introduced in the late 1800's, and metopon introduced in 1936, no true synthetic analgesic was reported before Eisleb and Schaumann developed demerol (1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride) *(19)*. Schaumann postulated that demerol, in its structure as a 4-phenylpiperidine derivative, constitutes a part of the morphine molecule *(56)*. Well-known in various countries under different names, its nonproprietary name is Meperidine. Demerol is used clinically in obstetrical and other analgesia in doses of 50 to 150 mg., orally or intramuscularly. Unfortunately, it is habit-forming *(4, 38)*.

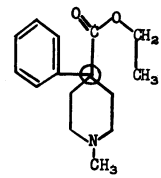
Structures, Syntheses, and Analgesic Activities. Eisleb condensed *N*-bis-(β chloroethyl)-methylamine with benzyl cyanide; the piperidinonitrile thus obtained was hydrolyzed and the carboxylic acid formed esterified with ethyl alcohol; the hydrochloric salt of this ester is demerol *(17, 18)*.



The configurational relationship between demerol and morphine is shown by the following structural formulas.



Morphine

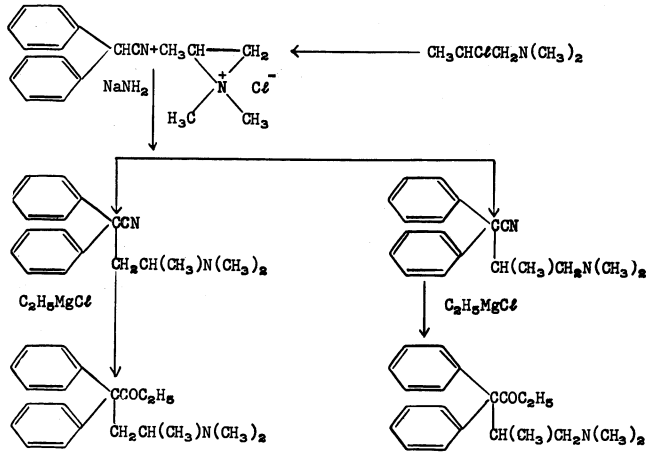


Demerol

According to Schaumann (*56*), the l-methyl-4-phenylpiperidine grouping with a quaternary carbon atom is the carrier of the analgesic effect of morphine. Other phenanthrene derivatives and phenanthrolines such as 2,7-dimethyl-4-hydroxy-5-methoxy-*p*-phenanthroline, although active in animals as an analgesic, show no typical morphinelike effects (*44*). A great number of demerol-like compounds have been prepared—e.g., the ethyl ester of the isomeric 1-methyl-3-phenylpiperidine-3-carboxylic acid (Metadine) which is active (*44*). Another analgesic of the morphine type is Hoechst-10720, now known as Cliradon-Ciba, a l-methyl-4-(*m*-hydroxyphenyl-piperidine)-4-ethyl ketone that is somewhat more potent than morphine (*18*, *43*).

Compounds that may be considered as reversed esters of demerol, especially the propionoxy derivative, have been prepared by workers of the Hoffmann-LaRoche Laboratories (*69*). One of these drugs has been marketed as Nisentil, formerly known as Nu1196. It is a potent analgesic and is used in obstetrics. Chemically, it is *dl*-α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride; it causes true addiction (*42*).

Another important development in the field of synthetic analgesics was the approach of Bockmühl and Schaumann during World War II, which culminated in the synthesis of amidon, also known as methadon, dolophine, adanon, and polamidon (*9*, *67*, *68*). While a potent analgesic in doses of 2.5 to 15 mg., orally, or 2.5 to 10 mg., subcutaneously and intramuscularly, it was found to cause true addiction. The synthesis, pharmacology, and clinical use of this compound have been reported repeatedly in the literature (*9*, *12*, *58*, *60*, *67*). The synthesis of amidon is as follows:



The synthesis takes its start from diphenylacetonitrile, which is condensed with 2-chlorodimethylaminopropane under the influence of sodamide. As this chloramine

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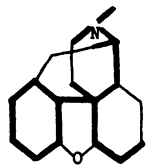
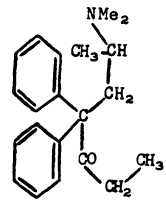
undergoes immediate cyclization to an ethyleneimine under these conditions, and the latter may react with diphenylacetonitrile in two ways, depending upon the cleavage of its three-membered ring, two isomeric nitriles are formed. After separation of the isomer, one nitrile yields amidon on treatment with a Grignard compound, while the other results in isoamidon upon similar treatment (*60*). The structural relationship of amidon to morphine (*7*) may be seen in the structural formulas.

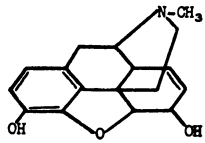


Morphine Fragment

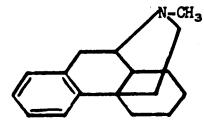


Amidon

The work of Grewe (*30*, *31*), of the University of Kiel, has contributed greatly to the old problems of the morphine synthesis and structure. Grewe found a relatively simple way to synthesize a basic structure analogous to morphine which he called *N*-methylmorphinan; their interrelationship (*33*) may be seen in the structural formulas (*34*).



Morphine



N-Methylmorphinan

The Grewe synthesis was carried out by condensing cyanoacetic ester and cyclohexanone–carboxylic ethyl ester in the presence of ammonium acetate, glacial acetic acid, and benzene. The condensation product was hydrolyzed with concentrated hydrochloric acid and the unsaturated dicarboxylic acid formed was heated with ammonium carbonate to form 1,3-dihydroxytetrahydroisoquinoline. Through chlorination with phosphorus oxychloride, the two hydroxy groups were removed and the dichloro compound formed was dechlorinated to yield 5,6,7,8-tetrahydroisoquinoline. The latter was methylated on the nitrogen and the reaction product interacted with benzylmagnesium chloride. Hydrogenation of the hexahydroisoquinoline derivative formed yielded 2-methyl-1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline which was cyclized to *N*-methylmorphinan using 50% phosphoric acid (*30*, *31*). An isomeric *N*-methylisomorphinan was prepared by Gates in a different way (*28*).

N-methylmorphinan has analgesic effects; however, its 3-hydroxy derivative was found to have potent analgesic properties. It seems that a tertiary nitrogen and the hydroxy group in the 3 position favor analgesic activity; the oxygen bridge of morphine does not seem to be essential (*30*, *31*). Schnider and Grüssner (*59*), of Hoffmann-LaRoche, synthesized 3-hydroxy-*N*-methylmorphinan in a manner similar to the Grewe synthesis. Its hydrobromide has been marketed as Dromoran and is used as an analgesic in doses of 2.5 to 5 mg., subcutaneously. Dromoran's analgesic effects in humans are somewhat better than those of morphine; the average duration of analgesia produced by Dromoran is somewhat longer than that produced by similar doses of morphine sulfate (*45*). It also causes habituation (*22*).

The synthesis of morphine has been the dream of organic chemists for a long time. It was finally accomplished in 1952 by Marshall Gates and Gilg Tschudi (*27*) of the University of Rochester, although parts of this total synthesis had been reported previously (*23–25*, *28*, *29*).

The initial material of the total synthesis was 2,6-dihydroxynaphthalene from which, in a complicated 10-step synthesis, 5,6-dimethoxy-4-cyanomethyl-1,2-naphthoquinone was prepared (*23–25*, *28*, *29*). A complete presentation of these steps was given by Marshall Gates before the 13th National Organic Chemistry Symposium, AMERICAN CHEMICAL SOCIETY, June 15, 1953, at Ann Arbor, Mich. (see page 8).

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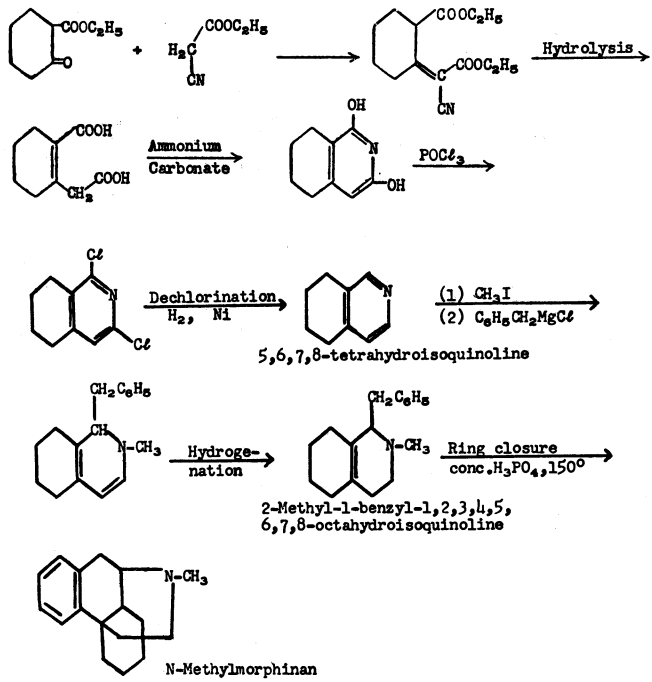

The naphthoquinone was subjected to the diene reaction with butadiene to form 3,4-dimethoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene. This was hydrogenated over copper-chromium oxide to give a ketolactam, which on Wolff-Kishner reduction and remethylation yielded another lactam. Reduction of the lactam with lithium aluminum hydride, followed by methylation with formaldehyde-formic acid, gave *dl*-β-Δ^6-dihydrodesoxycodeine methyl ether *(26)*. The racemate was resolved with L(+)-dibenzoyltartaric acid; the *d*-β-Δ^6-dihydrodesoxycodeine methyl ether, on hydration with dilute sulfuric acid, yielded β-dihydrothebainol methyl ether. On vigorous treatment with potassium hydroxide in diethylene glycol, demethylation occurred to yield β-dihydrothebainol. Oxidation of β-dihydrothebaino by a potassium *tert*-butoxide–benzophenone system gave β-dihydrothebainone. Bromination of this with 2 moles of bromine, followed by treatment with 2,4-dinitrophenylhydrazine, yielded a dinitrophenylhydrazone. Cleavage of the hydrazone with acetone and acid produced 1-bromothebainone. This substance was converted by catalytic hydrogenation to dihydrothebainone hydrate. Bromination of the latter with 3 moles of bromine, followed by treatment with dinitrophenylhydrazine, produced 1-bromocodeinone dinitrophenylhydrazone. On cleavage of this hydrazone, 1-bromocodeinone resulted. 1-Bromocodeinone was converted by lithium aluminum hydride in tetrahydrofuran solution into codeine. Codeine was demethylated to morphine, using pyridine hydrochloride as described by Rapoport and his coworkers *(53, 54)*. Thus, 146 years after the discovery of morphine by Sertürner, the first total synthesis of morphine was carried out.

Miscellaneous Analgesics. Aralkylamines have received attention as potential analgesic agents; of these, some sympathomimetic amines—e.g., epinephrine and ephedrine—have been reported to exhibit a pain-threshold-elevating action *(21, 51, 58)*.

More recently, a series of aminophthalidylalkanes, of which 1-amino-1-phthalidylpropane was the most active *(32, 66)*, was found to exhibit analgesic activity *(20, 67)*. Aralkylamines and aminophthalidylalkanes have not achieved any clinical importance.

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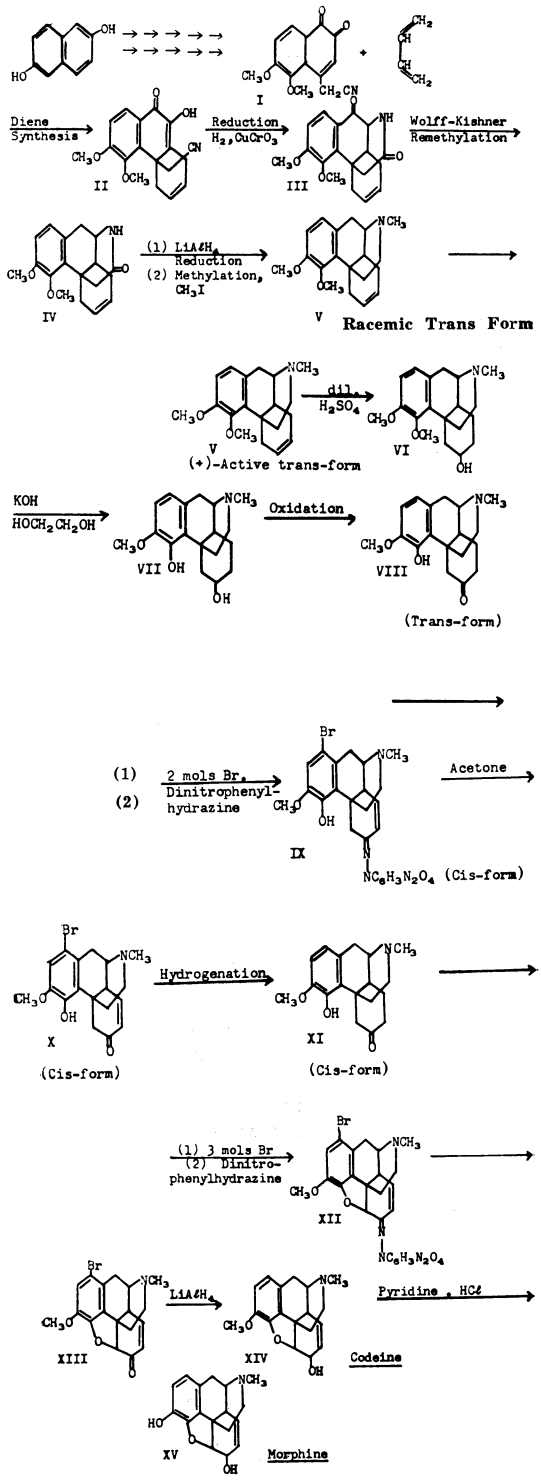

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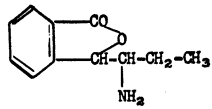
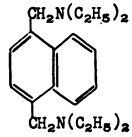
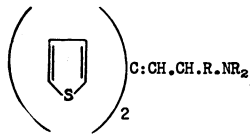


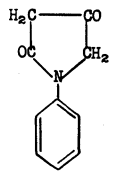
An interesting structure and rather unorthodox for an analgesic is 1,4-bisdiethylaminomethylnaphthalene hydrochloride. Reported by Badger and coworkers, it is claimed to have the same activity as demerol (*3*).



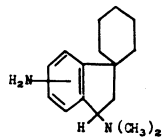
A series of potent analgesics, some of them as active as morphine in the rat, has been discovered by British workers of the Wellcome Research Laboratories; they are 3-tert-amino-1,1-(2′-thienyl)-1-butenes, where R = Me, Et; NR_2 = $N<[CH_2]_3>CH_2$, or $N<[CH_2]_4>CH_2$, or $N<[CH_2]_4>0$ (*1*).



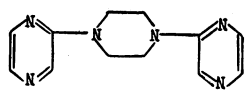
Büchi and coworkers *(11)* recently prepared several series of 3,5-dioxopyrazolidine derivatives. Some of them showed, in animal tests, analgesic effects on the order of pyramidon—e.g., 1-phenyl-3,5-dioxopyrazolidine.



Of several attempts to use the concept of quaternary carbon and tertiary nitrogen in β-relationship as a feature of analgesic potency, the interesting compound of Schwartzman (*61*, *62*) should be mentioned. According to Eddy (*16*), this material, a 1,1′-spirocyclohexyl-(?)-amino-3′-dimethylaminoindane, is stable and nearly twice as active as codeine (*5*, *16*).



Finally, 1,4-di-(2-pyrazyl)-piperazine, a "bissed" compound with an allegedly high analgesic potency, should be mentioned (*14*).



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Methods for Introducing Oxygen into Position 11 of the Steroids

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A survey is made of the various chemical, enzymatic, and microbiological methods developed to effect this oxygen addition. Investigations on the rare natural C-11 oxygenated steroids, such as sarmentogenin and gamabufotalin, are mentioned and the synthetic approaches are discussed under three broad subdivisions: (1) the shift to C-11 of a C-12 oxygen atom already present in the molecule (bile acids, hecogenin, etc.); (2) the actual introduction of an oxygen atom into those steroids which are devoid of oxygen in ring C and which form the bulk of the abundant naturally occurring compounds, and (3) the total synthesis.

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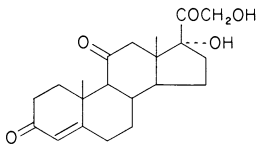
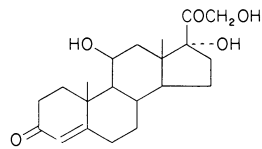
The first observations of the utility of cortisone in the treatment of rheumatoid arthritis by Hench and Kendall, in September 1948, not only opened up new horizons in medicine but also brought about a renaissance in the chemistry of steroids. The chemical problems arising from the need to make cortisone more plentiful and less expensive have been met successfully. The period of the last five years has brought forth many scientific publications attesting to the accomplishments of the chemist. Of the 28 steroids thus far recognized in adrenal cortex extracts, only 5 have been determined to be biologically active and only 2 are of medical interest at present. These are 11-dehydro-17-hydroxycorticosterone (otherwise known as cortisone) and 17-hydroxycorticosterone, now known as hydrocortisone.



Cortisone



Hydrocortisone

Steroids, widely spread through animal and plant life, have been known to chemists for a long time. Cholesterol, the unsaponifiable portion of animal and vegetable fats and oils, sex hormones, the bile acids, toad poisons, and many other substances usually found in small quantities throughout organic nature belong to this class of chemical compounds. Because these molecules are complex, their structure has been unraveled only in relatively recent times and much has yet to be learned about them.

From the molecular standpoint all of these substances can be considered as derived from a four ring structure made up of 17 carbon and 28 hydrogen atoms, technically known as cyclopentanoperhydrophenanthrene, each ring being identified by a letter and each carbon atom by a number as shown.

Instead of lying flat as might be inferred from the schematic representation, the bonds between the carbon atoms form angles in the third dimension, imparting a

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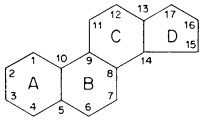
"puckered" structure to the molecule, which in turn is responsible for problems of steric hindrance that arise when attempts are made to attach other atoms to the system. This latter characteristic is particularly important, in that it influences the course of many reactions and often produces unexpected results. If, for example, a substituent or functional group is introduced in the improper spatial configuration, isomers of the desired compounds are produced which often are medicinally quite inactive. It seems to be essential for the C-10 and C-13 methyl groups (generally present in naturally occurring steroids) to project forward from the general plane of the ring system (assuming the so-called beta configuration, which is conventionally represented by a full line). In the natural steroids the same holds true for the hydrogen atom at C-8 and the side chain at C-17, whereas the C-9, C-14, and C-17 hydrogens assume the alpha configuration—i.e., they lie behind the general plane of the ring system and are usually represented by a dotted line.



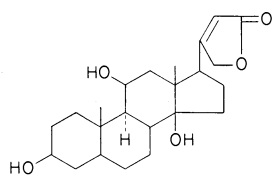
Since most of the natural steroids have configurations similar to that of cortisone, it seemed highly desirable to use one or the other of such natural steroids as starting material for a partial synthesis of cortisone. But, in addition to proper steric configuration, the antiarthritic activity of the adrenal hormones (whether synthetic or otherwise) appears to depend on the presence of certain functional groups at specified places in the ring system. Thus it would seem that there has to be: a double linkage between C-4 and C-5, oxygens at C-3, C-11, and C-17, and a basic $-CO-CH_2OH$ side chain. Absence of one or more of these substituents usually diminishes or completely eliminates the therapeutic value of the molecule.

C-11 Oxygen Function

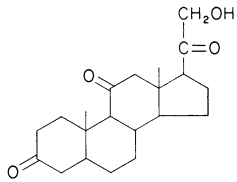
Of these groups, the C-11 oxygen function is perhaps the most interesting from the standpoint of steroid synthesis. A historical approach to the problem might make this more apparent.

The cortisone used by Hench was prepared from a bile acid, named desoxycholic acid, by means of a 30-step conversion process. Desoxycholic acid possesses an oxygen function in the form of an OH at C-12 which, through a sequence of reactions, was utilized as a "handle" to afford the desired C-11 keto compound. The vast amount of research effort responsible for this achievement, stemming from several laboratories across the country and drawing on the previous work of numerous other chemists, is partially reflected in nearly 250 pages of reports devoted to various aspects of this work *(36)*.

Following the discovery of cortisone's therapeutic value, it became immediately apparent that the supply of cattle bile would be inadequate, and a search for more abundantly available raw materials got under way. At first attention focused on the plant steroid sarmentogenin, because it possessed an oxygen function at C-11. As shown in a Dutch patent *(48)*, it can be converted into 3,11,20-triketo-21-hydroxypregnane, an important compound for the synthesis of cortisone.



Sarmentogenin



3,11,20-triketo-21-hydroxypregnane

While extensive plant expeditions by Swiss and American laboratories established that a number of *Strophanthus* species contain sarmentogenin, it became obvious that the agricultural program for the procurement of sufficient sarmentogenin would be too formidable to tackle.

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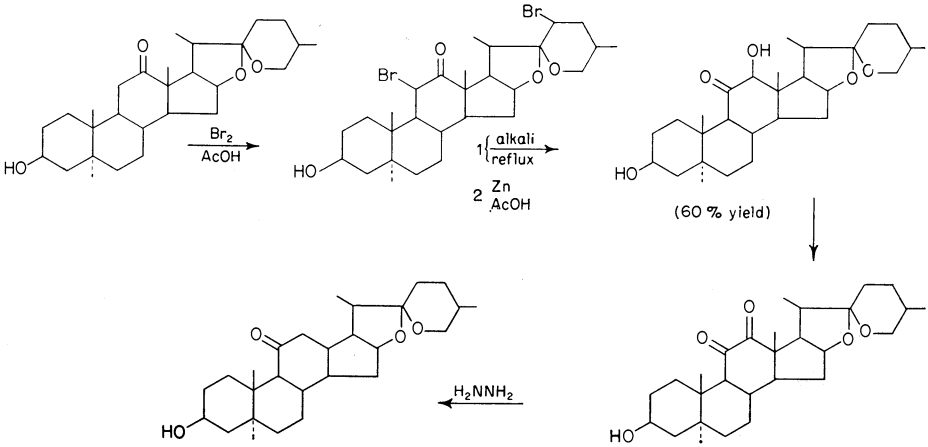
The sarmentogenin saga is entertainingly told in a chapter entitled "The Lost Strophanthus" in Burlingham's, "The Odyssey of Modern Drug Research," published in 1951 by the Upjohn Co. in connection with the opening of its new pharmaceutical manufacturing plant *(8)*.

Only one other natural steroid is known to possess an oxygenated C-11 and that is the toad poison, gamabufotalin *(44)*, of academic interest only.

Another plant steriod—the sapogenin hecogenin (chemically known as 22-isoallospirostan-3β-ol-12-one)—has received considerable attention because it contains oxygen in position 12. Hecogenin is readily isolated from certain species of *Agave* found in the southwestern parts of United States, Mexico, and Africa. It can also be easily recovered from sisal wastes.

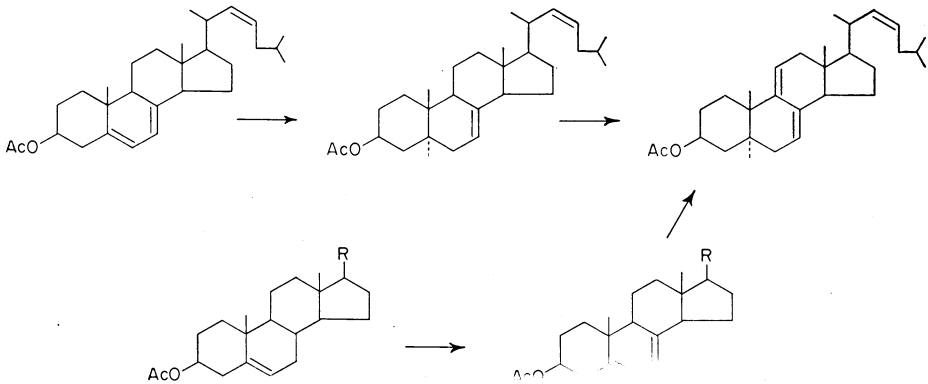
The conversion of hecogenin to an 11-keto compound (11-ketotigogenin) was accomplished by the group headed by Djerassi and Rosenkranz *(18, 19)* employing a modification of the scheme developed by Gallagher and his coworkers *(25)*.



The principal problem involved in this conversion is the transfer of the 12-keto group to the 11-position as shown.

Introduction of Oxygen Atom

In the meantime, attention had been turned to some of the steroids without oxygen at ring C that are readily available in relatively large quantities—e.g., cholesterol from wool fat, stigmasterol from many fats and oils, ergosterol from yeast, and certain sapogenins, in particular diosgenin which is readily obtainable from the Mexican yam, *Dioscorea macrostachya*. The object was to find practical methods by which oxygen could be introduced at C-11 in ring C. As so frequently happens in chemistry, the objective was realized in several laboratories almost at the same time.



A key intermediate in the utilization of these compounds is a conjugated 7,8:9,-

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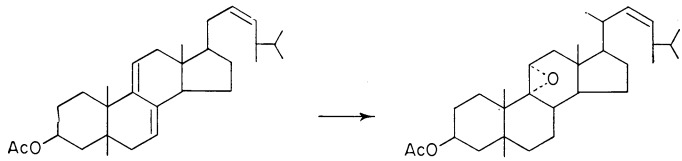
11-diene. These dienes are prepared from the 5,6:7,8-dienes by selective reduction of the 5,6 double bond followed by treatment of the 7,8-ethylene with mercuric acetate *(63)*.

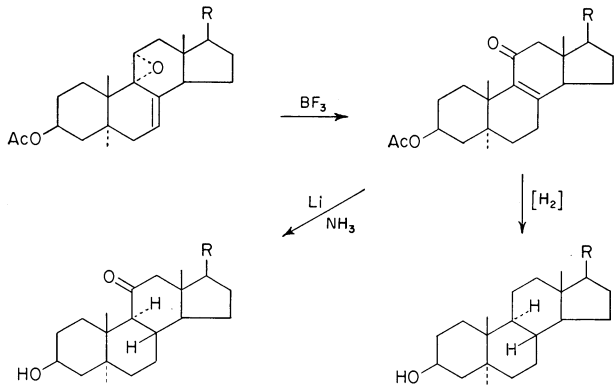
The 7,8 double bond (Δ^7) may be already present as in ergosterol or may be introduced into a Δ^5 steroid by the action of *N*-bromosuccinimide followed by dehydrobromination *(14)*. A process involving the shift of a double bond from position 6 has also been used *(13)*. The 7,9-dienes are interesting compounds; because they are conjugated, they span rings B and C, bridging positions 7 and 11.



For the conversion of 7,9-dienes, an interesting observation that the compound reacts with per acids in a stepwise manner was reported by Chamberlin, Chemerda. and coworkers *(10)* using ergosterol D and later by the Swiss group of Heusser and Jæger at Zurich *(32)*. The first mole of per acid is absorbed in a matter of minutes, the second in a matter of a few hours, and the third mole requires a day or so for consumption. By controlling the quantity of per acid a mono-, di-, and trioxide can be prepared.

Dichromate oxidation or hydrolytic rearrangement of the monoepoxide followed by oxidation affords the 7-11-diketo-Δ^8 compound which is converted to the 11-ketone by zinc dust and acetic acid, followed by removal of the 7-keto group by a Wolff-Kishner reduction *(22)*.

Of the many other reactions that the monoepoxide is capable of undergoing, the following *(55, 58)* is most interesting for the synthesis of cortisone.



This rearrangement was first reported by Swiss investigators and observed independently in the Merck laboratories *(32, 55, 58)*. When the oxide is treated with boron trifluoride or aluminum chloride (in benzene), it is rearranged into a $\Delta^{8,9}$-11-keto derivative. The reduction of the 8,9 double bond occurs readily with lithium in liquid ammonia, the desired configuration at position 8,9 being obtained. The yield is 90% or better. If alcohol is present during the reduction, the 11-keto group is also reduced to the 11α-hydroxyl group. As these methods are most direct in the utilization of the oxide, they are preferred.

Two other attractive routes to 11-keto steroids from the same 7,9-dienes were reported by Stork and others *(59)* and Djerassi and others *(16)*. Stork and coworkers obtained a 9,11-epoxy-7-keto compound which, on treatment with alkali, rearranges to the corresponding $\Delta^{8,9}$-11α-hydroxy-7-keto compound. The 8,9 double bond is readily reduced, yielding the 7-keto-11α-hydroxy steroid. The 7-keto group was eliminated by the Wolff-Kishner reaction or through the thioketal with Raney nickel.

Djerassi and coworkers converted a $\Delta^{8,9}$-7-keto steroid into the enol acetate,

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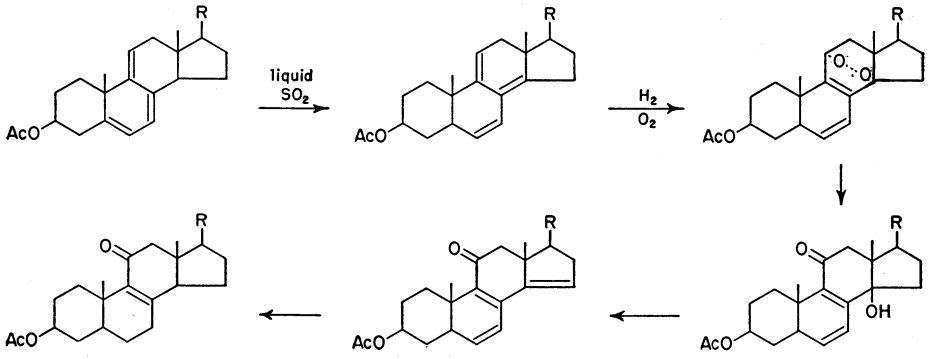
which was oxidized with perphthalic acid to the $\Delta^{8,9}$-7-keto-11α-hydroxy compound *(16)*.

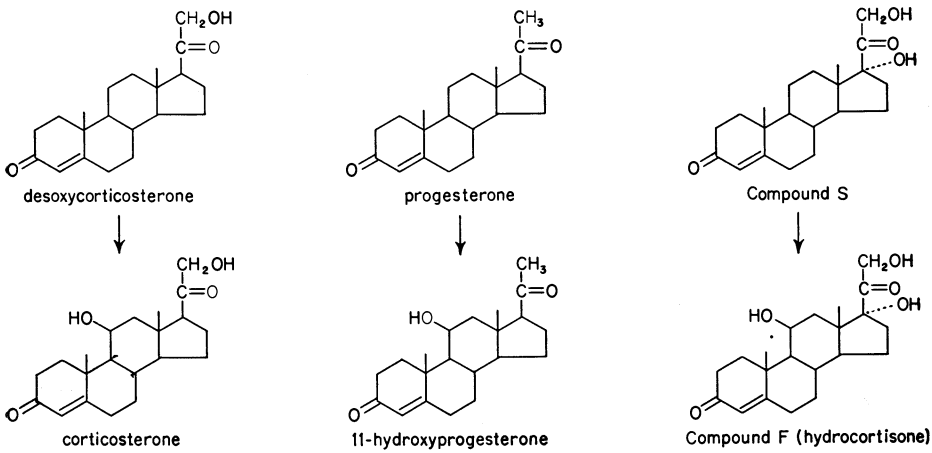
A departure from the $\Delta^{7,9(11)}$ approach was announced by Laubach and coworkers *(39)*, who employed photochemical peroxidation of ring C dienes to introduce the 11-oxygen as a C-11 to C-14 peroxide bridge.



A dehydroergosterol-type triene is catalytically isomerized with liquid sulfur dioxide to yield the $\Delta^{6,8(14),9(11)}$-triene, which is then photoperoxidized and the resulting transannular peroxide is rearranged with mild base to the 11-one, 14-hydroxy compound. Dehydration followed by hydrogenation affords the $\Delta^{8,9}$-11-keto steroid.

With regard to biological methods for C-11 oxygenation, a new line of attack was opened by the observation of Hechter, Pincus, and others *(65)* of the Worcester Foundation for Experimental Biology that perfusion of sterols (such as Compound S and desoxycorticosterone) through the adrenal gland causes hydroxylation in position 11, to produce hydrocortisone and corticosterone.

This discovery was further extended by this group to cover a number of steroids including progesterone (to yield 11β-hydroxyprogesterone, corticosterone, and hydrocortisone), Compound S (to yield hydrocortisone), cholesterol (to yield a mixture of cortical hormones), etc.



It was later found by others *(41, 55)* that homogenates of the adrenal gland are also effective in bringing about the 11-hydroxylation reaction. In every case, hydroxylation produced an 11β-hydroxy steroid which one expects, since the 11α-hydroxy steroids have not been found in the glands. Although these reactions can be carried out in vitro and are remarkable to the organic chemist, they have not been considered completely practical because of the limitation of adrenal gland supplies and the instability of the enzyme system. Up to now no direct chemical oxidation has been devised to carry out this step. If the human gland can carry out 11-hydroxyla-

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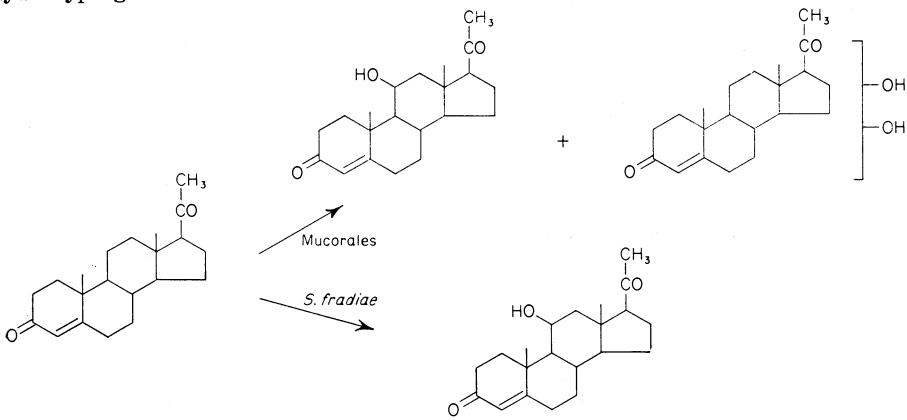
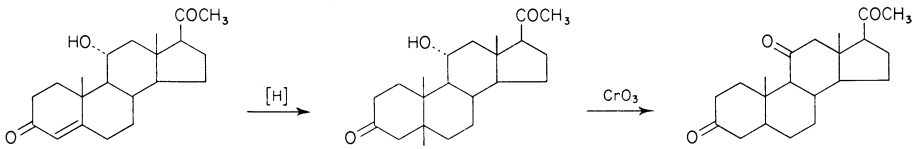
tion reactions and the chemist cannot furnish the reagent to accomplish this same transformation, possibly the microbe may provide the tool.

In April 1952, Peterson and Murray of the Upjohn Research Laboratories *(50)* reported that steroids can be 11-hydroxylated using microorganisms. Thus, a common mold of the order of Mucorales *(Rhizopus arrhizus)* oxidizes progesterone to 11α-hydroxyprogesterone and to a dihydroxyprogesterone, later found to be 6α,11α-dihydroxyprogesterone.



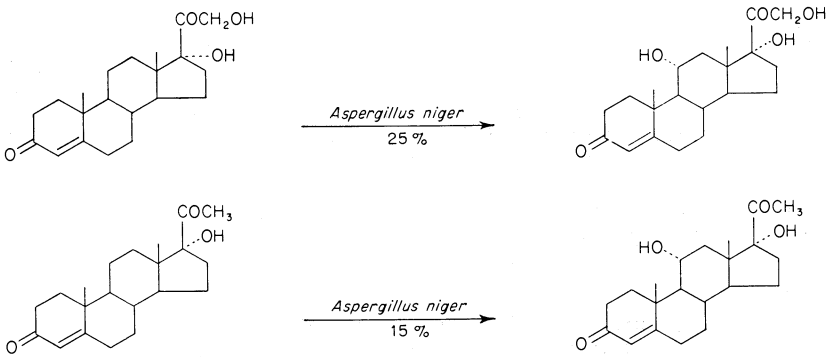
The Upjohn publication was followed by several publications on the use of microorganisms for steroid hydroxylations *(12, 24)*. Using an unidentified fungus of the Rhizopus family, the Syntex group *(40)* carried out the microbial oxidation of progesterone to 11α-hydroxyprogesterone in 45% yield. The same authors converted 11α-hydroxyprogesterone to pregnane-11,20-dion-3α-ol acetate which previously had been converted to cortisone.



This synthesis from progesterone requires 10 steps or, starting with diosgenin, 14 steps required. It is the shortest synthesis of cortisone (starting with a plant material) reported to date.

The Squibb research group *(24)* observed that *Aspergillus niger* is also effective in microbial oxidation of steriods.

The same hydroxylation was carried out with 17-hydroxyprogesterone. With the latter, the expected 11α,17α-dihydroxyprogesterone was obtained (15% yield) along with 17α-methyl-D-homo-Δ^4-androstene-11α, 17α-diol-3,17-dione (25%).



The microbial oxidations described above produced in all instances the unnatural 11α-hydroxy derivatives. Colingsworth *(12)* reported that *Streptomyces*

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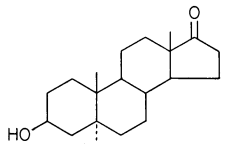
fradiae converted Compound S to hydrocortisone in small yield. In this instance 11β-hydroxylation occurs and similates the adrenal gland in this respect.

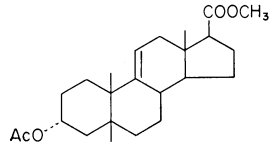
Microorganisms are capable of hydroxylating certain steroids in other positions than the 11 and 6 positions. Thus, Perlman, Titus, and Fried *(49)* observed that an unidentified actinomycete oxidized progesterone to 16α-hydroxyprogesterone. A dihydroxyprogesterone as yet unidentified was also formed.

Total Synthesis

Three groups of workers have now completed total syntheses of steroidal compounds capable of being converted into cortisone. Robinson in 1951 *(9)* succeeded in synthesizing epiandrosterone. Simultaneously Woodward *(64)* and his associates at Harvard University announced the successful synthesis of methyl-3α-acetoxy-$\Delta^{9(11)}$-etiocholenate.



Epiandrosterone

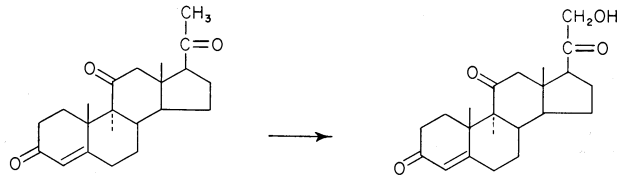


Methyl-3α-acetoxy-$\Delta^{9(11)}$-etiocholenate

These syntheses intersected previously published partial synthesis of cortisone from natural occurring steroids and hence constitute the first formal total synthesis of cortisone.

A complete total synthesis of cortisone by an uninterrupted series of reactions was accomplished by Sarett *(54)* and coworkers of Merck & Co., Inc. The following chemicals were put together in a stereospecific manner to yield the 21-carbon atom skeleton of cortisone: ethoxypentadiene, benzoquinone, methyl vinyl ketone, methallyl iodide, and ethoxyacetylene magnesium bromide.

The benzoquinone furnished the 11-oxygen atom of 11-keto-progesterone, which was the first steroid intermediate obtained in this synthesis. This was converted into dehydrocorticosterone and then into cortisone. In this synthesis *dl*-cortisone was prepared as well as the natural stereoisomer.



11-ketoprogesterone → Dehydrocorticosterone

Conclusion

Today a number of different practical methods are available for the synthesis and production of 11-oxygenated steroids. All these methods are only a little more than 2 years old as far as scientific publications are concerned. They have in part been responsible for the widespread availability of cortisone. Today cortisone is available in every hospital and corner drugstore in this country and in many other countries. This rapid development from the "laboratory curiosity" of 3 years ago to the stage of widespread availability is a tribute to modern technology and assures the ultimate goal—the availability of this drug to everyone who needs it.

The following bibliography gives additional references to the methods of introducing oxygen into position 11 of the steroids.

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Literature of Radioactive Pharmaceuticals

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It has been slightly more than ten years since man's initiation of the nuclear chain reaction, and only about seven years since the first shipment of a pile-produced radioisotope. In that short time these isotopes have not only become an integral part of medical practice, but have proved most valuable research tools. Many industrial groups, including some in the medical field, have set up groups to employ these new techniques safely. One of their very important functions is to survey the widely scattered reports, evaluate them technically, and sell management, as well as their fellow research workers, on the advantages to be gained by employing isotopes for selected problems. Abbott has gone further and developed as a part of its research department a division having to do with the development, production, and distribution of radioactive pharmaceuticals conforming to and tested by good pharmaceutical standards.

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When it is realized that only a few months more than 10 years ago the first nuclear chain reaction was made to take place under the stands in Stagg Field, one can only be astonished at the progress that has been made in this field. The difficulties have been many. First of all, there came wartime secrecy, and then the necessity for keeping many of the data classified. Almost equally important has been the fact that it has been necessary to train, almost from scratch, groups of highly specialized research workers. Only in the past 5 years has adequate instrumentation been commercially available. Some of the pitfalls and unusual problems presented by isotope studies are just beginning to be appreciated. It cannot be emphasized too strongly that isotopes themselves, and their use, are no guarantee of successful experimentation. In fact, much of the evidence in the biological field is contrary to what would have been anticipated on the basis of older theories.

Perhaps the most striking phenomenon is the growth of a group of hybrid scientists. We, of course, had the biochemist and physical chemist, but we now have the biophysicist, the health physicist, the radiation chemist, the radiobiologist, and a host of analogs whom Brucer grossly calls "isotopologists." It is typical of this development that the younger, and sometimes some of the older, men in a given field have acquired training in this new field and have applied this new knowledge to their own fields of specialization.

In industry, for instance, many companies have groups of specialists working with isotopes, but always welcome the suggestions of others who think they see in radioisotopes new avenues of research approach. It is thought to be the right plan for men with ideas and technical skill to come to the isotope group, with its background of specialized equipment and radiation protection, work with it for as long as may be necessary to prove or disprove their points, and then return to their regular fields of activity.

This situation is very definitely reflected in the chemical literature of radioisotopes.

Journals

Except perhaps for *Nucleonics* (which is rather unfortunately tending more and more to the physics side), there is no really specialized journal in this field. A fairly complete resume of the references on radioactive isotopes appearing in *Nu-*

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clear Science Abstracts and the *Current List of Medical Literature* between January 1952 and June 1953 shows that references appeared in more than 600 publications. The *Journal of the American Chemical Society* contained one of the largest number of references.

It was at one time felt that this field was rather closely allied to the work of the radiologist. Yet an analysis of the reports shows that *Radiology* and the *American Journal of Roentgenology* carried fewer such publications than a number of other journals, particularly those in the biochemical and physical fields.

Obviously, the diverse places of publication make it practically essential to rely, for the most part, and certainly in the medical field, upon abstract journals or abstract publications to keep in touch with the latest developments. As always, *Chemical Abstracts* is doing a very excellent job, but here again it is necessary to cover many pages in order to be reasonably sure of comprehensive coverage. In that respect *Nuclear Science Abstracts*, which is now in its tenth volume, deserves special commendation. This is an official publication of the U. S. Atomic Energy Commission through the Technical Information Service at Oak Ridge, Tenn.

Perhaps the most valuable single feature is a listing of all unclassified and declassified reports from the many agencies and contracting laboratories of AEC as well as the corresponding European atomic energy installations, some 50 in all. Most of these are subsequently reported in very brief form as abstracts.

The availability of each report included in *Nuclear Science Abstracts* is indicated in its abstract. Declassified reports may be purchased through the Office of Technical Services in Washington, they may be obtained from the agencies issuing them, they may be borrowed from cooperating AEC libraries, or they may not be available for distribution.

Of particular interest is the fact that the abstracts covering biology and medicine, chemistry, engineering, metallurgy, physics, etc., are carried under these headings. It thus becomes possible in a reasonable amount of time to check leading articles.

Two extensive bibliographies on the literature of radioactive isotopes are worthy of mention. The first is a bibliography of more than 400 references which appeared in connection with the article, "Radioisotopes in Pharmaceutical and Medical Studies," in the November and December 1950 and January 1951 issues of *Nucleonics*. The second is an annotated bibliography of radiobiology released by the Technical Information Service of the U. S. Atomic Energy Commission at Oak Ridge.

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Books and Manuals

There are a reasonable number of books which should be in every library. These include the University of California series on "Advances in Biology and Medical Physics," Hahn's "Manual of Radioisotope Therapy," Low Beer's "Clinical Use of Radioactive Isotopes," Siris' "Isotopics Tracers and Nuclear Radiations," and Kamens' "Radioactive Tracers in Biology."

From time to time manuals on various specialized fields such as gold therapy and brain tumor localization have been issued by Abbott Laboratories.

Delay in Publication. In connection with publication, there have been two very serious problems. The first is delay. Articles submitted somewhat more than a year ago are currently coming to press in magazines like *Radiology* and the *Journal of the American Roetgenologic Society*, whose official title is the *American Journal of Roetgenology, Radium Therapy*, and (as of last year) *Nuclear Medicine.*

A second and somewhat "sore point" is the fact that a great deal of work in this field is centered about method development. In general, synthetic procedures must be directed toward a specific end and the greatest possible economy of a given isotope. With certain short-lived isotopes, the time required for carrying out a given reaction and the isolation may be the deciding factor. In others, the ability to carry out a certain synthesis with a minimum of handling and radiation exposure to the operator may be the crucial point.

To the nonisotopic editor, burdened with problems of space limitation, these modifications seem relatively unimportant, and too many contributions which would have served a real purpose in the furthering and enhancement of synthetic proce-

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dures have been turned down as "unoriginal." They may be unoriginal, but they are certainly not unimportant.

Recent Highlights

Radioactive Gold. Foremost is the use of radioactive gold. While this has actually been in use for three years, the articles are just beginning to come through. The author's group has just finished compiling the "Gold Manual." This contains some 85 references, to which another 15 could easily be added since that time.

The radiation from the x-ray machine or from radium is essentially gamma radiation which is, statistically speaking, a very poor agent for destroying cancer cells. In fact, as Paul Aebersold pointed out in an article appearing in a recent radiological magazine, if radium had been discovered as a part of this isotope program, it probably would never even have been very seriously considered for therapeutic application.

On the other hand, the beta rays from artificial radioisotopes are characterized by a very limited degree of penetration, with the utilization of their entire energy over a very thin layer. This has advantages, and some disadvantages. On the positive side, it is possible to destroy the thyroid, and only one instance in the entire medical literature has been found where the immediately adjacent parathyroid has even been temporarily damaged. On the other hand, if we wish to irradiate the entire mass of a tumor, and most materials do not localize as does the radioiodine used above, it becomes necessary to try to infiltrate that area as uniformly as possible.

This is a difficult situation, and one for which there is no very simple answer. Yet the fact remains that today the use of radioactive gold infiltrated by direct administration into the prostate of men with prostate cancer offers one of the best possibilities of prompt alleviation, and perhaps even a reasonable percentage of permanent relief, from that disease.

Even more important is the use of gold, given intrapleurally or intraperitoneally. Here its radiation does not penetrate more than the surface of the tumor or the peritoneal wall. It has very little effect upon the tumor itself, but it does definitely stop, in somewhere between 50 and 75% of the cases, the very detrimental accumulation of ascitic or pleural fluid associated with breast and ovarian malignancies. In other words, it is not a cure, but it does give, in a reasonable percentage of cases, more months of fairly comfortable and occasionally even active life.

Radioiodine. One of the earliest chemical reactions tried with radioiodine was its incorporation with proteins. As most proteins contain tyrosine residues, it is possible to iodinate them. Many reports have appeared, but it is only within the past 2 years that we are beginning to understand the proper means of iodination, so that the material retains to the maximum degree its naturalness as far as the body is concerned. It thus becomes possible to use such a tagged albumin for very simple determinations of both blood and plasma volumes, and to do this repeatedly and successfully upon the same patient over a period of time.

Very surprisingly, this same material, which we call RISA, localizes in brain and certain other tumors, and the gamma radiation therefrom may be used as a diagnostic test for the presence or absence as well as the exact localization of such brain tumors. It has been employed instead of Lipiodol to study where blocks have occurred in the spinal canal. Even more interesting, and of probably considerable more importance, is its use for studying circulation. In other words, if one has one scintillation counter pointed over the heart and another at the sole of the foot, and gives a dose of albumin very rapidly, it becomes possible to determine the time required for circulation between the heart and the foot. It is thus possible to detect derangement of circulation, all very quickly and harmlessly.

This same material, given orally instead of intravenously, is digested just like any protein, and it would seem that a fairly simple determination of the iodine output is a fairly sensitive index of pancreatic enzyme function.

Here, then, it would seem as if we had a fairly universal "reagent" which could well be kept on hand in many biological and clinical research laboratories for the many uses to which it can be successfully applied.

Radioactively tagged compounds have been extensively used for the study of drug metabolism. Some results have been good, some disappointing; but at least they

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have altered materially our conception of drug distribution and handling within the body.

Hypnotics. During his earlier days, the author may have been frequently guilty of pointing out that the hypnotics exerted their action by localizing in the central nervous system. Studies carried out with radioactive Pentothal, radioactive Nembutal, and their analogs show that this is not at all true. Actually there may be less Nembutal in the brain than in the surrounding plasma. We are beginning to recognize still another disturbing factor—the fact that a given barbiturate may actually be present in the bloodstream is no indication that it is in an active form. As Taylor and Richards of these laboratories recently reported, the effect of liver dysfunction on the duration of action of barbiturates may not depend upon a difference in the rate of metabolism, but rather upon a difference in the amount of proteins in the blood. The more protein, the more barbiturate is held in inactive form, and the less is available for the exerting of its action.

Isonicotinic Hydrazide. Everyone is very much interested in the isonicotinic hydrazide or isoniazid. This has been made tagged with carbon-14 in the carboxyl group by the group at Los Alamos and studied extensively at the University of Chicago. As seems to be true with almost every drug, there was a fairly general distribution in the body, with the blood, skin, and lungs each having about 5% of the total administered activity at the end of half an hour. At the end of 8 hours a large portion of this had disappeared. The only major metabolite found was isonicotinic acid itself. It was possible to show that this material penetrated into enlarged caseous nodes relatively easily and that detectable amounts remained there for as long as 4 days. Very recently this same group has reported upon the use of the tagged material in humans. Again excretion was fairly rapid, some 85% the first 24 hours. Highest tissue levels were found in the lungs and skin, with concentrations in actual lesions somewhat, but still not too much, higher than in other tissues. It could be established that such concentrations were theoretically sufficient to produce bacteriostasis for a number of days, and it was concluded that this factor, plus the ability of the drug to permeate into the lesions and the accompanying diseased tissue, was responsible for its clinical activity.

In a very recent paper it has been shown that *Tuberculosis bacilli* susceptible to isoniazid become radioactive when grown in a medium containing carbon-14–labeled isoniazid, while resistant bacteria do not.

Insulin. The Lilly group employing pure cystine prepared by Abbott Laboratories actually labeled insulin with sulfur-35. Such methods are, of course, laborious. Stadie and his group at the University of Pennsylvania have been able to iodinate insulin as well as to prepare an insulin sulfate, both of which seem to retain their activity essentially unchanged. Gleason of the Abbott Laboratories likewise succeeded in producing iodine-tagged insulin of a very high degree of purity. It was shown by three methods that both types are bound by strong, presumably chemical forces, by various tissues, such as the rat diaphragm. This group feels that the activity of the insulin observed is a function of the quantity bound in close association with, not a part of, enzymatic systems.

Sucaryl. Sometimes it is best to ask simple questions of specifically designed radiosotope experiments. For instance, it became highly desirable to know how the new sweetening agent Sucaryl is handled by the animal body. Extensive chemical work had resulted in a recovery of only about 50% of the injected material, and as a result restrictions were imposed on the amount used in any given day. Very fortunately, a very smooth synthetic procedure was developed for sulfur-labeled Sucaryl. Taylor and his group at Abbott were able to show that it is very rapidly eliminated from the body completely unchanged. This seemed to satisfy the Food and Drug Administration and as a result all limitations have been removed. Its usefulness in a wide variety of fields, including dietetic foods and even diabetic beverages, is rapidly on the increase. At least the resultant revenues have helped pay for the many "unprofitable" ventures of the department.

Penicillin G. The group is just at the "turning point" of another valuable contribution in the antibiotic field. It has developed very satisfactory microbiological procedures for one incorporation of sulfur-35 as sulfate directly into penicillin G. This material has been used by two laboratories for fundamental studies on the mechanism of antibiotic action. It has also been used by a leading agricultural

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school in experiments on cattle and milk production. By employing this sulfur-labeled penicillin, and a method of isotope dilution, we have still another accurate, and certainly noncontroversial, method of penicillin-G assay.

Selenium Residues. There is still another way in which isotopes can be very useful from the analytical side. While there is every indication as to the safety of Selsun, a new selenium sulfide preparation for seborrheic dermatitis, there is naturally extreme interest in how much of the material might be left on the skin, on the hair follicles, under any given set of conditions. Analytical procedures for selenium, in this form, are just not applicable.

If a skin sample containing a totally unweighable amount of such a selenium sulfide residue is taken and placed in one of the more active piles for a few hours, the selenium is converted to a radioactive form. In spite of the fact that its half life is only 15 to 20 minutes, it is possible to use radiochemical methods rather than straight chemical methods for the assay. The same techniques have been applied by our nutritional group to arsenic assays on tissues of animals whose growth had been promoted by arsanilic acid.

One of the earliest uses of radioisotopes was in connection with the study of the human antithyroid activity of certain compounds. The results were extremely clean cut, and at variance with the result which had been determined earlier upon animals.

One of the most interesting and certainly one of the most controversial subjects appearing in the literature is the mechanism of radiation damage to the body. In view of the possibility that we ourselves may some day be caught in an atomic bombing raid, this becomes an extremely important and practical problem.

Fortunately, Abbott Laboratories has chosen to keep its work as a part of the Research Department, and has welcomed collaborative efforts not only with medical research groups but with good friends in the pharmaceutical industry as well. To cite but one example, Smith, Kline, and French have supplied very pure synthetic thyroxine and triiodothyronine which is labeled with iodine-131 and supplied to all interested groups with pooling of information as it becomes available.

Reference File. From the very beginning of the project, some 7 or 8 years ago, a fairly up-to-date reference file has been kept, not of all subjects, but primarily those of interest in the biological and medical field. Three resumes appeared in *Nucleonics* for 1950–51, and if the number of reprints requested is any criterion, it aroused considerable interest.

At about this same time the laboratory distributed a very complete list of all titles in this field appearing during that year. This did not prove to be anywhere near as valuable or as practical. As a result, instead, several progress reports were supplied to all collaborators and those specifically requesting them. These deal with the principal subjects of interest and, in not more than two pages, survey the current status of that particular use or project. These contain a reasonable number of references and, again to judge from the interest, have proved valuable. This is now being enlarged to include, not all references, but only those additional ones most likely to prove of value to research workers and to clinical investigators. The selection is somewhat arbitrary, but any pertinent omissions can easily be incorporated in the next edition if the subject has grown in interest.

While perhaps not in the field of "literature," the group has been interested in the education of prospective isotope workers in the medical field. The radioactive pharmaceutical plant in Oak Ridge, the only institution of its kind in the world, is always open to qualified visitors.

Literature on Radioactive Isotopes

The literature references of interest to those working in the field of radioactive isotopes which appeared in *Nuclear Science Abstracts* and the *Current List of Medical Literature* during the period January 1952 to June 1953 were tabulated in order to find which serial publications carried the greatest number of articles on this subject. References appeared in more than 600 publications.

The publications listed below covered the greatest number of articles on radioactive isotopes.

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Medical Journals, American

American Journal of Physiology
American Journal of Roentgenology
Cancer Research
Journal of the American Medical Association
Journal of Cellular and Comparative Physiology
Journal of Clinical Endocrinology and Metabolism
Journal of Laboratory and Clinical Medicine
Journal of the National Cancer Institute
Journal of Pharmacology and Experimental Therapeutics
Mississippi Valley Medical Journal
New England Journal of Medicine
Proceedings of the Society for Experimental Biology and Medicine
Radiology

Scientific Journals, American

Analytical Chemistry
Archives of Biochemistry and Biophysics
Canadian Journal of Chemistry
Journal of the American Chemical Society
Journal of Biological Chemistry
Journal of Chemical Physics
Journal of Physical Chemistry
Nucleonics
Science
X-Ray Technician

Medical Journals, Foreign

Acta Radiologica
Acta Unio Internationales Contra Cancrum
British Journal of Radiology
British Medical Bulletin
Bulletin de l'Association Française pour l'Etude du Cancer
Fortschritte auf dem Gebiete der Roentgenstrahlen
Journal Belge de Radiologie
Journal de Radiologie et d'Electrologie
Radiologia Medica
Radioterapia, Radiobiologia e Fisica Medica
Strahlentherapie

Scientific Journals, Foreign

Analyst
Analytica Chimica Acta
Bulletin de la Société chimique de France
Journal of the Chemical Society (London)
Comptes Rendus de la Société de Biologie
Doklady Akademii Nauk, S.S.S.R.
Nature
Naturwissenschaften
Zeitschrift für anorganische Chemie
Zeitschrift für Naturforschung

Research Reports

AECD Reports. Atomic Energy Commission. Declassified Reports.
AECU Reports. Atomic Energy Commission. Unclassified Reports.
BERE Reports. Atomic Energy Research Establishment, Harwell, England.
ANL Reports. Argonne National Laboratory
BNL Reports. Brookhaven National Laboratory
NP Reports. Atomic Energy Commission Nonproject.
NYO Reports. New York Operations Office, Atomic Energy Commission.
UCLA Reports. Radiation Laboratories, University of California, Los Angeles.
UCRL Reports. Radiation Laboratory, University of California.
UR Reports. Atomic Energy Project, University of Rochester.

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Recent Publications

Atomic Energy Commission

"Eight-Year Summary of Isotope Distribution," March 1955, contains more than 7000 references, divided into 30 fields of work. Includes author index.

Book TID 4000, February 1955, provides a cumulative numerical list of available unclassified USAEC reports.

The Isotope Division has released bibliographies covering the recent literature on several of the more widely used isotopes (I^{131}, P^{32}, Au^{198}, etc.).

Abbott Laboratories has published at approximately 6-month intervals bibliographies and resumes covering current developments, both published and unpublished.

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A Critique on Literature of Antituberculous Compounds

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Because of the successes achieved with the sulfones, streptomycin, *p*-aminosalicylic acid, and the benzenoid thiosemicarbazones, the search for new and better compounds has been broadly extended in many laboratories and the literature of antitubercular compounds has grown enormously in recent years. Unfortunately, in vivo activity—the standard, which all compounds must meet before being judged suitable for clinical application—has not been applied to the classification of antitubercular compounds in the literature. In this situation, remedial measures appear to be called for and some corrective suggestions are advanced.

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The chemotherapy of tuberculosis, in the modern sense of the term, dates from 1939. In that year, Rist *(11)* and his coworkers *(12)* demonstrated for the first time, the in vitro and in vivo efficacy of 4,4'-diaminodiphenylsulfone against the hitherto apparently impregnable tubercle bacillus. On this basis, the literature of modern, antituberculous compounds covers at most a period of the last 14 years. This is not meant to imply that the chemotherapy of tuberculosis was not attempted prior to 1939 or that the number and range of substances used against tuberculosis were insignificant. Practically everything which had ever demonstrated activity against any disease was tried in tuberculosis.

In the Decennial Index of *Chemical Abstracts* for 1927 to 1936, a partial listing of the substances which were reported to have been used or tried in the treatment of tuberculosis includes antisera, calcium chloride, calcium ions and calcium compounds in general, camphor, cod liver oil, copper and copper compounds, chaulmoogra oil, cholesterol, cinnamic acid, coramine, ethyl stearate, ferric chloride, formates, gold salts, iodides, sodium ricinoleate, manganese salts, proteins, phenol, quinine, rare earth compounds, the vitamins from A to D, and tannins. These are among the more conventional therapeutic substances reported during that ten-year period. Less conventional perhaps but certainly of no greater efficacy was the recommendation of one investigator *(10)* that tuberculosis patients eat 100 to 150 grams of semiraw spleen daily as an important adjunct to gold salt therapy. This recommendation was based on the temperature and weight benefits demonstrated by two cases, which is a rather inadequate basis for any claim. As medieval as the use of the splenic preparation may sound, it is futuristic in comparison to the use of charcoal or pulverized animal carbon by injection *(2)*. And yet, as recently as 1933, the intravenous administration of carbon for the treatment of tuberculosis was warmly defended *(7)*.

Judging from some of the substances listed, the chemotherapy of tuberculosis prior to 1936 appears to have been based on the premise that if the patient could survive the drug, he could survive the disease. Actually, the uncritical and unrestrained use of anything that came to hand was indicative of the long and desperate need for effective antituberculous agents. Every clue, whether real or imaginary, was eagerly followed and phthisiologists were prepared to try the most unorthodox procedures in the hope of favorably influencing the course of the disease.

In surveying the literature on antituberculous compounds immediately prior to 1940, it is difficult to realize that some of the papers were written only a few years ago—so great has been the progress in the last decade. For example, in 1936, in the

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Bulletin de la société de chimie biologique, two investigators *(4)* reported that persons living near a salt lake in the vicinity of Tekirghiol, Dobrodgea, were wont to treat rickets and tuberculosis by coating the patients with the black mud and slime of the lake shore. The bedaubed patients were then required to dry out in the sun. According to the investigators, the mud, rich in algae and therefore in ergosterol and other sterols, may owe its beneficial effects to the irradiated ergosterol which is absorbed presumably through the skin.

The dearth of chemotherapeutants in 1937 is evidenced in a review article by Johnston *(8)* on the pharmacology of some newer drugs employed in tuberculosis therapy. The review lists barbiturates, calcium compounds, and some newer gold salts. In 1940, Jotten and Reploh *(9)* wrote that Solganol B-oleum and auric taurocholate T226, bismuth with curcum dye, copper in the form of Bayers' "Ebesals" and the benzyl esters of chaulmoogra fractions gave the best expectations for the successful chemotherapy of tuberculosis. In effect, therefore, the literature of antituberculous compounds of true chemotherapeutic significance covers at most the period from 1939 to the present. Certainly none of the compounds which were widely used and accredited before 1939 are now accepted as effective tuberculostats. This was pointed out by D'Arcy Hart in an excellent review of the chemotherapy of tuberculosis covering the 100-year period prior to 1939 *(5)*. According to him, by 1935, a general reaction had taken place among the clinicians against antituberculous drugs with the exception of a few valued symptomatics. This reaction was a somewhat belated recognition by the phthisiologists that most of the drugs used were without scientific basis and that the few drugs originating in scientific laboratories were transferred to clinical application on inconclusive evidence. Browning *(3)* in a 1935 lecture on chemotherapy stated, "No treatment at present can be aimed directly against the causal agent . . . "

The literature of antituberculous agents is not confined to any one scientific sphere. Progress in chemotherapy is the product of a joint enterprise involving several scientific disciplines. In consequence, the pertinent publications on antituberculous compounds are scattered through the chemical, biochemical, biological, pharmacological, bacteriological, medical, antibiotic, and general science literature. Since this critique is addressed to and directed toward chemical investigators, discussion is confined to those papers which deal with the chemical nature of tuberculostatic compounds and the laboratory evidence for their activity.

Discussion

The chemotherapy of tuberculosis had fallen into disrepute by the middle thirties because the drugs used up to then were of highly questionable efficacy and had been placed into clinical use without being firmly based on convincing and favorable laboratory experiments. The advent of the sulfones not only ushered in a new class of tuberculostats but also paved the way for a new philosophical approach to the chemotherapy of tuberculosis. The era of the uncritical application of untested substances to human guinea pigs is passed and general recognition is given to the need for extensive and thorough laboratory experimentation before clinical trial. This change of view was aided greatly by the fact that the sulfones were the first compounds to show marked in vivo activity against the tubercle bacillus. With the knowledge that the "impossible" had been achieved and that the "impregnable" tubercle bacillus could be controlled within the protective environment provided by the host, a new criterion was established for tuberculostatic substances. Proof of in vivo activity has become a prime requisite to clinical application.

Because of the successes achieved with the sulfones, and later with streptomycin, *p*-aminosalicylic acid, and the benzenoid thiosemicarbazones, the search for new and better compounds has been broadly extended in many laboratories throughout the world and the literature of antituberculous compounds has grown enormously these past few years. In tacit acknowledgment of the trend, *Chemical Abstracts*, in its 1947 index under the heading, "tuberculosis," used for the first time the subheading, "antitubercular compounds." Unfortunately, the standard of in vivo activity which all compounds must meet before clinical application has not been applied to the classification of antitubercular compounds in the literature. Currently, no distinction is drawn in literature classifications between in vitro and in vivo activity. Since the compounds with in vitro activity are legion and far exceed in numbers those with in vivo activity, the literature of antitubercular substances is rapidly

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being cluttered with reports on compounds which do not merit the classification, "antitubercular."

Without regard to the pros and cons of the in vitro test as a screening procedure, compounds with only in vitro activity should not be classed as "antitubercular." If the view is accepted that the purpose of research in the chemotherapy of tuberculosis is to find compounds with clinical potentialities, then standards must be established by which such compounds should be judged and these standards should be applied to classification in the literature as well as in the laboratory. The number of compounds active against the tubercle bacillus has grown to the point where serious consideration need only be given to those compounds which possess significant activity in experimental tuberculosis and only compounds of this latter class should be called "antitubercular." Yet any survey of the current literature finds a large number of papers purporting to deal with antitubercular compounds but which, in reality, list compounds that are either totally inactive or are active only in vitro. This is well illustrated by an analysis of the items listed under the heading, "tuberculosis," subheading, "antitubercular compounds," in the *Chemical Abstract* Index for 1951. Of a total of 19 papers surveyed, 12 papers deal with compounds whose activity has been tested only in vitro, five papers with compounds tested in vivo and two papers do not list activity at all. In two of the 12 papers based on in vitro studies and in two of the five based on in vivo studies, all of the compounds reported are inactive. In effect, therefore, only three of 19 papers purporting to deal with antitubercular compounds actually report on chemotherapeutically active agents. To those interested in the chemotherapy of tuberculosis, there would appear to be an overabundance of chaff with the wheat.

This is not to be interpreted as a denunciation of those papers which report on inactive compounds or on compounds whose activity has only been tested in vitro. There is a definite place in the scientific literature for all publications which add to the general knowledge. The problem is one of classification and not of exclusion. Therefore, the mere mention of the word "tuberculosis" in a chemical paper should not qualify it for classification in the literature of antitubercular compounds. A case in point is the paper by Basu and Banerjee entitled, "A Therapeutic Agent in Tuberculosis" *(1)*, in which the authors reported on the preparation of the phthaloyl derivative of *p*-aminobenzaldehyde thiosemicarbazone. The compound was prepared presumably as a less toxic substitute for Tibione. Regardless of its ultimate merits, the fact remains that the report does not mention either biological experiments or activity. Therefore, the compound may or may not be active, but the designation "therapeutic agent" is not warranted. Strictly speaking, the paper properly belongs in the category of organic preparations. Similarly, in another paper *(6)*, a number of *p*-aminophenylazole derivatives substituted in the azole ring were prepared in connection with the investigation of the "dependence of tuberculosis-inhibiting action on structural factors." The activity of none of the compounds is listed and there is no assurance that they are active—yet they are classified among the antitubercular compounds in the index of the *Chemical Abstracts*.

Another source of confusion is usually encountered in review articles on the chemotherapy of tuberculosis. Authors of review articles sometimes fail to distinguish between in vivo and in vitro activity and in so doing invest some compounds with unmerited importance. For example, Stenlake *(13)*, in an excellent review listing over 230 references and covering the literature between 1939 and 1950 inclusively, states:

Heterocyclic sulfones such as promizole (4,2′-diaminophenyl-5′-thiazolylsulfone), diphenyl and heterocyclic sulfides and sulfoxides, diphenyl ethers, diphenylamines and diphenylmethanes possess tuberculostatic activity. With the exception of promizole, few of these compounds have progressed beyond the stage of testing in experimental animals.

Actually, the diphenyl and heterocyclic sulfides, the diphenyl methanes, and most of the diphenyl ethers have been tested only in vitro, and the diphenylamines, though tested in vivo, were too toxic to permit an in vivo effect to be observed. In short, these classes of compounds are not truly antitubercular and grouping them with the sulfones tends to confer on them an unwarranted significance.

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Suggestions for Literature Classification

In view of the inevitable growth of the literature on antituberculous compounds, the inclusion of so much irrelevant material promises to be a severe handicap to future workers in the field and measures should be taken to correct the situation. The execution of such remedial measures devolves mainly upon the journal editors but the authors can do much to make the literature of antitubercular compounds more meaningful to the laboratory or literature researcher.

The following definitive steps in the right direction are suggested:

All authors should be required to confine the adjective antituberculous (or antitubercular) to those compounds that show activity in experimental tuberculosis—preferably with the human or with the bovine strain of tubercle bacillus.

The titles of papers in which the activities of the compounds are not given should not suggest chemotherapeutic application unless some properly qualifying term is included. For example, the paper by Basu and Banerjee should not have been entitled, "A Therapeutic Agent for Tuberculosis," because no statement is given on activity, either in vivo or in vitro. A more correct title would have read, "The Synthesis of a Compound to Be Tested in Tuberculosis." Better still, all reference to tuberculosis in the title should have been omitted.

The classification of compounds in indexes should separate and clearly distinguish between in vivo activity and in vitro activity. Under the heading, "Tuberculosis," *Chemical Abstracts* should have two subheadings: "antitubercular compounds" for those active in vivo and "in vitro active compounds" for those whose testing has not progressed beyond the in vitro stage or for those active only in vitro and not in vivo.

Review articles should also carefully distinguish between in vitro and in vivo active compounds. To be in accord with convention, reviews on the chemotherapy of tuberculosis should include only those compounds which have been chemotherapeutically—i.e., in vivo—tested.

A further suggestion to those who contemplate working in the field is to concentrate their attention on those publications dealing with in vivo active compounds and save for leisure reading those which report only in vitro activities. Adherence to this principle has served the author very well these past few years and has been an excellent guide through the maze of publications to those of most significance. In this regard the review articles have been particularly valuable in highlighting the more fundamental and more concrete contributions to the chemotherapy of tuberculosis. Therefore, a list of six review articles providing a fairly complete coverage of the entire field until early 1953, is appended to the literature cited.

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Introductory Comments Concerning Pharmaceutical Trade-Marks

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Comments are given concerning the importance and development of pharmaceutical trade-marks.

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The importance of names to those working with pharmaceutical and medicinal literature is obvious and requires no comment. As many as three totally distinct types of names may be applied to a drug. One is the chemical or scientific name which often denotes accurately the structure of the compound. Another name usually, but not always, used on drugs is the proprietary name or the trade-mark. A third is the nonproprietary name, sometimes also referred to as a generic or common name.

A trade-mark is a name or device adopted and used by a manufacturer or merchant to designate the goods that he manufactures or sells and to distinguish them from those manufactured or sold by another. The trade-mark functions as an indication of origin, so that, regardless of whether the purchaser sees the trade-mark in New York or San Francisco, the goods are associated with the same proprietor. Trade-marks also function as a guarantee of uniform quality so that from previous experience the customer knows whether to buy—or avoid. A third function performed by a trade-mark is that of selling. Through advertising, the mark becomes established in the mind of the purchaser; it comes to his mind automatically when he is shopping. Trade-marks function also in providing ready-made markets in case a manufacturer desires to extend his market to new or allied products to be sold under the same trade-mark. Thus, trade-marks are property representing great investment, and may be of great value. Consequently, the owner does his utmost to establish his trade-mark by every means at his command. The possibility of establishing a "trade-mark" is one of several considerations which induce manufacturers to engage in research for the development of new and improved products.

Registering of Trade-Marks

Trade-marks are secured by adoption and use. The creation of pharmaceutical trade-marks requires essentially the same techniques as in any other industry, so that reference need be made only to a few unique features. One of these is the service provided by the two industry associations, The American Drug Manufacturers Association and The American Pharmaceutical Manufacturers Association, by the operation of a Combined Trade-Mark Bureau with which member firms may register trade-marks. The names are then published and distributed to members, any of which may object if their own trade-marks are resembled too closely. In this way, trade-mark searches, in which there is a large subjective element, are supplemented by the review of many others and an opportunity is provided to iron out differences of opinion on an informal basis with saving of time, effort, money, and good feelings.

Developing Trade-Mark Names

In developing trade-marks, it sometimes is necessary to compromise conflicting points of view. Thus, the advertising and sales people often tend to favor descriptive or suggestive names because such names are believed to be established more easily. Names may be suggested resembling the leading product in the field. The trade-mark attorney does not like a descriptive name because it is a weak trade-mark.

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If the company depends heavily on the medical profession, medical contacts oppose therapeutically suggestive names which the medical profession dislikes.

Another factor is the attitude of the American Medical Association which suggests that certain principles be followed, such as conformance to accepted rules of nomenclature. Examples are the "ol" suffix to indicate alcohol or phenol, "ine" to indicate amine, and so on.

Those concerns operating in international trade try to develop names suitable for use in the various languages. Two instances illustrate a type of hazard encountered. One firm markets a product under the name Privine. It is a good product and has sold well. Probably no adult American reared in a rural area, once having heard the name, would forget it and, in that sense, it is a good name. Recently this same firm was looking for a trade-mark for its Pyribenzamine nebulizer. Pyribenzamist seemed a very nice name but, in German, "mist" means "manure."

Loss of Trade-Marks

Trade-marks may be lost unless care is used in their adoption and use. Court decisions have held that, lacking a suitable nonproprietary name, a trade-mark may lose its trade-mark status and become a nonproprietary name. Consequently, the trade-mark owner must always create a suitable name which can be dedicated to the free use of the public. In this respect, the pharmaceutical industry does not differ from others but, in this industry, agencies such as the American Medical Association, the various pharmacopeia commissions, and the World Health Organization take an active interest in selection and use of nonproprietary names.

Improper use of trade-marks also may result in damage to trade-mark status of a mark, and for this reason, trade-mark owners are sensitive to improper use. Trade-marks are proper nouns, a point which should be borne in mind by authors of scientific papers. While formerly trade-marks did not appear in the *Journal of the American Medical Association*, now they not only appear, but are marked as trade-marks.

Those dealing in international trade may encounter difficulty because the pharmacopeia commissions in various countries select different official nonproprietary names. Confusion and added expense are caused by the duplication in labels, cartons, and promotional literature.

Again, in international trade, the trade-mark owner faces the problem of pirating in some countries wherein the first to register controls the name. A United States manufacturer may find both his trade-mark and the nonproprietary name registered in such countries.

The trade-mark owner does his best to establish his trade-mark. In this effort some opposing pressures may be faced—for example, the medical profession looks with disfavor on the multiplicity of trade-marks for a given product because of the difficulty of remembering them, and the retail druggist dislikes a large number because it increases his inventory. Some merit exists in this criticism—for example, recently, in making a search, approximately 50 names beginning with the syllables "Cor" and "Cort" were encountered.

Conclusion

Those in the pharmaceutical industry who are concerned with "trade-marks" would make two requests, that writers in the scientific literature treat trade-marks as proper English words—e.g., by capitalization—and that those coining trivial names which eventually may become nonproprietary names make a search in order to avoid close similarity with either trade-marks or other nonproprietary names.

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Generic and Brand Names for Drugs

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The expanding number of complex chemical compounds for medicinal use requiring the application of convenient generic names, and the multiplication of brand names, increase the difficulty of selecting distinctive terminology for new drugs. The use of dissimilar generic names by different authorities or by different countries further aggravates this problem. Organizations adopting generic names and pharmaceutical manufacturers seeking trade-marks share in the responsibility for developing new terminology.

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Generic names for drugs can be defined as recognized nonproprietary designations, available for unrestricted use, which are unprotected or for which trade-mark rights have been waived. When adopted for legally recognized publications, such as the "U. S. Pharmacopeia" or the "National Formulary," they are frequently referred to as "official" names and may be so identified by affixing the abbreviation for those publications, U.S.P. or N.F. When adopted by the Council on Pharmacy and Chemistry of the American Medical Association prior to their admission to the "official" publications, they may be referred to as "council-adopted." When they are included only in the council's annual publication, "New and Nonofficial Remedies," the abbreviation N.N.R. may be affixed. Reference also can be made to the generic terminology adopted for pharmacopeias or their equivalents that are published in other countries.

Brand names may be defined as trade names (including those protected as trademarks) that are applied to different drug products by individual manufacturers. The multiplicity of brand names for well-known drugs has magnified the difficulty of coining additional brand names as well as generic terminology for new drugs. Some pharmaceutical manufacturers employ a single trade name for each drug, whereas others coin a different brand name for each additional salt or dosage form of the same drug that is introduced on the market. The vast array of trade-marks for various penicillin salts and dosage forms is a monumental example of the confusion which results from this practice. Manufacturers defend it on the basis that the physician wants a short name or symbol to simplify prescribing, whereas the doctor complains that the identity of the particular drug is difficult to recall for prescribing because there are so many names.

Origin of Generic Names

Generic names may originate in published reports of individual investigators as well as in those of scientific organizations responsible for the selection of appropriate drug terminology. Some names, such as penicillin, bacitracin, and streptomycin, were suggested by their discoverers. Occasionally, the surname of the discoverer may figure in the coining of a name as a means of honorary recognition, although this method of identification is more often applied to the naming of various living forms than to the naming of drugs. Antibiotics such as penicillin and streptomycin were named on the basis of the microbiological source from which they are derived. The name bacitracin was selected to honor a seven-year-old patient named Margaret Tracey from whom the discoverer isolated the strain of *Bacillus subtilis* which produces the antibiotic.

The scientific departments of drug manufacturers also frequently propose or

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introduce generic terms that are recognized by the council and other agencies responsible for the selection of drug nomenclature. Indeed, the majority of generic names for drugs considered by the council are initiated by proposals of pharmaceutical manufacturers. The council encourages such cooperation prior to the placing of new drugs on the market so that satisfactory terminology can be employed at the outlet, including early use of accepted terminology in the medical literature; thus, generic names, rather than trade names, code numbers, or less convenient chemical names, can be used in scientific reports on new compounds. When new drugs are referred to repeatedly only by experimental numbers, abbreviations, or the systematic chemical name, such designations tend to acquire "generic" status, in the sense that they represent the only "common or usual" name as interpreted under the labeling provisions of the Federal Food, Drug, and Cosmetic Act.

Similarly, when only a brand name has been used to identify a drug, it may gradually lose its ownership status under the amended trade-mark law and come to be regarded as a generic term. The name aspirin is in this category, and because of greater convenience, it is generally preferred over the official designation, acetylsalicylic acid. Likewise, the repeated use of the abbreviation BAL (British Anti-Lewisite) has hampered the establishment of the more chemically descriptive pharmacopoeial name, dimercaprol.

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Generic *vs.* Chemical Names

Simplified generic names are becoming more imperative as the number of complex chemical compounds introduced for medicinal use is expanded by systematic research. With simple inorganic compounds, such as ferrous sulfate, systematic chemical names are sufficiently easy to remember and convenient for use in speaking and writing; it is both unnecessary and undesirable to coin other designations when simple chemical compounds are employed as drugs. For such compounds, simple chemical names are to be preferred as generic names. However, the coining of contracted names, such as epinephrine or procaine, for complex organic compounds is essential to replace the systematic but unwieldy chemical nomenclature. When properly coined and properly introduced into scientific literature, short generic names for complex compounds then become synonymous, by definition, with the complete chemical terminology, and can be used conveniently in place of the latter, even in chemical publications. Whenever practicable, it is desirable to coin generic names that bear some recognizable resemblance to systematic chemical terminology. Thus, some effort should be made to provide a terminal suffix, such as "ol" for an alcohol or phenol, to connote accurately the type or class of chemical to which the compound belongs.

Similar attention should be given to systems of nomenclature for other basic sciences, as in the selection of names for biological and other substances which cannot be completely defined chemically. If possible, generic names also should be so coined that they avoid any misleading connotation as to identity. Thus, the "ol" suffix in the adopted designation cyclocumarol is somewhat misleading for a derivative of coumarin which does not contain a hydroxyl group. When chemical identification is partially or wholly obscured, a suitable designation usually can be adopted on the basis of current knowledge. For example, the name vitamin B_{12} has been used pending the development of the chemically derived term cyanocabalamin. However, as in the case of the chemically derived generic designations for certain other drugs, some time is required to displace the early terminology and there may be some confusion.

Isomeric Chemical Compounds

A special problem arises in the selection of generic names for chemical compounds capable of existing in several isomeric forms, two or more of which may exhibit promising pharmacological properties. In such instances, it may be desirable to anticipate the introduction of several isomers of the same compound in devising a name for the first one made available for clinical use. Until recently, attention to this aspect of generic terminology has received little consideration. Thus, the "official" designation epinephrine for *l*-epinephrine does not connote the levo isomer to which it refers, whereas the term arterenol, formerly employed to

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designate the levo isomer of norepinephrine, has been expanded recently to levarterenol to indicate its stereoisometric identity. The name methadone likewise does not suggest the racemic *(dl)* form of that analgesic compound, although this may be considered to be understood as it is for amphetamine. While the matter is of greater importance to chemical taxonomists than to physicians or pharmacists, consideration is warranted so that confusion between drug and chemical terminology is avoided. In many instances, where not more than one or two forms are found to have clinical use, the particular isomer in the names need not be specified particularly if other terminology has become firmly established.

Misleading Names

Generic as well as brand names, except those for serums and vaccines, should be coined to avoid any obvious connotation of diseases for which they are to be used. Physicians who do not wish to reveal to patients the nature or purpose of a prescribed remedy would find this difficult if obliged to use therapeutically suggestive names for prescribing drugs. Another inherent objection to such names lies in the possibility that they may become misleading if the drugs to which they are applied are found to have other uses. Misleading names can lead to dangerous confusion in dosage or method of administration. The further significance of the suggestiveness of names is illustrated by certain classes of drugs which have acquired pharmacological connotations through long association with a particular scheme of terminology. For example, the "caine" ending, usually employed for naming local anesthetic agents, has been applied whether or not it accurately reflects a strictly correct chemical classification of all such compounds. The misleading "al" ending, long employed for naming barbiturates as well as other sedative agents, is also in this category. Thus, through long usage the connotation of sedative action inherent in the "al" suffix tends to pre-empt its application to an aldehyde unless that type of compound happens to have some sedative or hypnotic action. Despite the inaccurate connotation of the "al" ending when used in names for nonaldehyde compounds, its association with barbiturates cannot be effaced readily. For these reasons, in the naming of isomers, efforts to improve imperfect drug nomenclature already established should be approached with caution to avoid provoking further confusion.

Problems in Drug Nomenclature

Although some of the older generic terminology is admittedly longer and more difficult to learn than a catchy trade name, its use offers ultimately less of a burden to the memory than attempting to recall one of a variety of trade names, some of which may apply only to particular dosage forms of the same drug. Often, however, the first trade name introduced gets a "head start" on other names, including the generic name, with the result that a new drug becomes better known by its brand name than by any other terminology. Physicians who wish to use only generic names for prescribing can specify a particular manufacturer's product when desired by affixing the name of the firm to the generic name of the drug.

The recent trend to adopt more convenient generic names for drugs may encourage their more general use and discourage the use of ambiguous symbols in place of established nomenclature. The multiplication of generic names for the same drug presents less of a problem than it does for trade names. Nevertheless, the existence of more than one generic name or synonym also tends to create confusion, particularly in the scientific literature.

The difference in generic names for drugs used in various countries has led to the creation of a Subcommittee on International Nonproprietary Names of the World Health Organization. This agency seeks to recommend common generic terminology for drugs on a world-wide basis, through the cooperation of its member countries, although in certain instances domestic conflicts cannot be avoided. In some cases conflicts of international names with domestic trade-marks are involved. The unfortunate occurrence of trade-marking generic names outside the country of origin presents an international problem. The efforts of the World Health Organization and of the Combined Trade-Mark Bureau of the American Drug Manufacturers Association and the American Pharmaceutical Manufacturers Association to discourage this practice are highly commendable, but so far these have met with only partial success.

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Future Outlook

For the future, a more judicious attitude toward the introduction of brand names on the part of the pharmaceutical industry is desired to avoid further aggravation of the problem of selecting distinctive generic terminology for new drugs. Some manufacturers have found it expedient to reuse old trade-marks formerly applied to abandoned products. When this practice results in the application of a name to another drug, further confusion is created, especially if the name already has appeared in published literature on the drug to which it was formerly applied.

The problem of finding nonconflicting terminology cannot be solved through the reuse of old names. The difficulties must be met by more frugal use of trade-marks and a cooperative attitude in the selection of uniform generic nomenclature; otherwise, the vast storehouse of terms that can be derived from the language eventually may become exhausted. The mutual efforts of responsible agencies on nomenclature, both here and abroad, provide encouragement that improvements in drug terminology will parallel the advance of future therapeutic discoveries.

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International Nonproprietary Names

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A program for selecting nonproprietary names for drugs through international cooperation is conducted by the World Health Organization, with its object being to minimize the discrepancies in common names for drugs existing between nations. The organization of the project and progress as well as fundamental and controversial difficulties are discussed.

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A chemist's success in conceiving and synthesizing a new compound which proves valuable as a drug not only opens great opportunities scientifically but also imposes weighty responsibilities. These remarks are directed to singling out the responsibilities concerned particularly with pharmaceutical nomenclature.

It is important that each new drug come on the market with two unique names. One of these is the brand or trade name, which should be registered for the exclusive use of the interested firm. Such a name is deemed to be better if it is easily recognized and remembered. The second name is the trivial or nonproprietary name, which need not have the qualities desirable in a brand name but should indicate something of the chemical nature of the drug. While this is a nonproprietary name, available for free and unrestricted use, it too may be registered. Frequently, however, the struggle of finding the brand name is so exhausting that no serious effort is made to find a nonproprietary name at first. This failure invites future trouble, the most serious kind of which is the possibility that the brand name will come into such common use as to lose its exclusive, protected status. The best known examples of this are the names aspirin and cellophane.

From the standpoint of the world market in drugs another source of difficulty looms larger. It resides in the probability that different nonproprietary names will come into use for the same drug. The resulting confusion benefits no one and is a nuisance in drug commerce. It means that, in the face of a multiplicity of trademarks, the one possible common key to identity is lost. The greatest confusion is in the hindrance to the interchange of scientific information, both experimental and clinical. The complications of abstracting and cataloging are also serious. Finally, differences in nonproprietary nomenclature can only result in a higher cost of doing business.

The only means of avoiding multiplicity in nonproprietary nomenclature for drugs is through international action, in spite of all the obstacles that obstruct the paths in that direction. The problem bears on public health generally, so that the World Health Organization has undertaken to bring about order and uniformity on an international scale. As a unit of the United Nations and the successor to the Health Organization of the League of Nations, the WHO alone is in a logical position to assume this role. It may be debatable whether the menace to world health from confusion over drug nomenclature is to be ranked with such pressing problems facing the WHO as the eradication of tuberculosis, malaria, and other deadly diseases. Furthermore, the funds of WHO are limited. The fact is, however, that WHO has established a program aimed at recommending, for international adoption, a single, nonproprietary name for each drug likely to move in international commerce. In 1955, an arrangement was completed for naming compounds capable of producing addiction even though they may not have been introduced commercially as drugs. This action facilitates the important task of the United Nations body responsible for the international control of traffic in narcotic agents.

Program of World Health Organization

A rather full discussion of the mechanics of the program has been published *(1, 2, 4–6)*. Briefly, the project is directed by the WHO Secretariat in Geneva, Swit-

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

zerland, with the advice of a Subcommittee on International Nonproprietary Names consisting of four individuals, from areas of the world having a very real interest in the subject. Until recently these four were: Hans Baggesgaard-Rasmussen, Royal Danish School of Pharmacy; Rene Hazard, School of Medicine, University of Paris; C. H. Hampshire, retired secretary of the British Pharmacopoeia Commission; and the writer. In 1953, Robert T. Stormont, secretary of the Council on Pharmacy and Chemistry of the American Medical Association, replaced the writer on the subcommittee. As with all WHO experts, these serve on a voluntary basis without pay.

In the United States, coined, common names for drugs are usually spoken of as "generic" names but this practice is not followed elsewhere. Hence, the WHO chose the term, *nonproprietary*, instead of *generic*, to designate names not covered by trade-mark rights. Since primarily the word "generic" means classification according to genus and genera, there is no doubt that "nonproprietary" is a more specific and less ambiguous term, although less convenient. Specificity is a highly desirable attribute, considering especially the necessity for translation into several languages.

Since Latin is still regarded as the universal language of medicine and pharmacy, the primary form of the international nonproprietary name is Latin with the English and French equivalents given secondarily in parallel in all WHO publications.

The program was established in 1950 and the subcommittee set up rules of nomenclature patterned almost exactly after those followed by the Council on Pharmacy and Chemistry of the American Medical Association and the British Pharmacopoeia Commission. These rules have been published and are generally known; they are considerably more flexible than those of the Scandinavian Pharmacopoeial Council which adopts names for use in the four Scandinavian countries and Iceland.

Not until 1953, did the American pharmaceutical industry take an active interest in the WHO program, although three years earlier the American Drug Manufacturers Association had given it enough attention to pass a resolution upon it. This earlier action was not recalled during the protest campaign which ultimately reached the floor of the World Health Assembly in its annual session in May 1953. The result was a very beneficial re-examination of the entire program with a restatement of its aims and procedures, which had evolved piecemeal in the first 3 years of the program's operation.

The protest campaign was spearheaded by the two leading trade associations of the pharmaceutical industry, the American Drug Manufacturers Association and the American Pharmaceutical Manufacturers Association, which enlisted the support of other organizations including the United States Pharmacopeia. The complaint was on the grounds that there was insufficient opportunity for drug houses to comment on proposed names and that no procedure was established for appealing decisions in those cases where the name adopted by the WHO was deemed objectionable or detrimental to trade-mark rights.

These complaints were unquestionably justified. Not only was the program inadequate but its operation on an informal plane was simply not compatible with the magnitude of the interests concerned. Some of the drugs on which agreement was not readily reached had a business volume running into tens of millions of dollars a year, as in the case of Terramycin which came out with oxytetracycline as its international nonproprietary name.

Structure of World Health Organization

The lack of opportunity to comment on proposals was directly related to the organizational structure of the WHO. The body is set up to maintain contact with each of the member states, the 81 nations of the world which have full or associate membership, through the respective official correspondents, generally the Ministers of Public Health or as here, the Surgeon General of the U. S. Public Health Service. Suggestions, complaints, and appeals for WHO assistance all channel in through these correspondents. The Director-General of WHO is guided in responding to many of these communications by experts who advise in a completely independent capacity according to their best individual judgments. Their recommendations then flow out from WHO through the same official correspondents. This means that for

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each country, all nationals, private citizens, and multimillion-dollar drug firms alike are expected to be kept informed mainly over a single line of communication.

With nonproprietary names for drugs, the proposals were being received freely enough but movement in the opposite direction left much room for improvement. Drug firms were not learning that names were being sought for their products until the process of selection had gone too far for lodging protest. No clear avenues of appeal had been provided. Further, the whole area is one in which little international law has yet been established. Special measures were taken to circulate the proposed names regularly through the *Bulletins of the Combined Trade-Mark Bureau.* It proved that the American pharmaceutical industry was not alone in benefiting from this publication of the WHO proposals. At least two trade papers reprinted them as news items and the effectiveness of this publicity was attested by comments received here from as far away as Holland and Australia. All such comments were forwarded to the WHO Secretariat in Geneva for transmission to the other members of the Subcommittee on International Nonproprietary Names. Nevertheless, the American drug industry felt that this relatively prompt but informal system was inadequate and unfortunately no effort was made elsewhere in the world to duplicate it.

The procedure now in effect calls for even more extensive publication of the names in the American pharmaceutical press. Further, some restrictions have been laid down and an appeal process is spelled out.

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Procedure for Proposals of Nonproprietary Names

In brief, the new procedure calls for submitting proposals for Recommended International Nonproprietary Names on a regular form to WHO as in the past. The proposals are forwarded from the Secretariat in Geneva to the subcommittee for consideration with the understanding that the original name shall be accepted unless there are "compelling reasons to the contrary."

The rules adopted in 1954 embody important changes in the original rules:

The clause ". . . unless there are compelling reasons to the contrary" is employed in connection with adopting the name coined by the person discovering or first developing the drug in question. There remains room for debate as to what constitutes a "compelling" reason but obviously trivial reasons are ruled out. The greatest potential source of difficulty arises in this connection from the differences in attitude toward nonproprietary names existing between nations. In the United States no special pressure has been exerted in the past to select names that will have a reasonable chance of competing with the brand name for the same drug. Elsewhere, particularly in England and Denmark, a great deal of attention is given to adopting nonproprietary names as short and euphonious as brand names generally are.

Names under consideration are to be published in the *Chronicle of the World Health Organization (3).*

A 4-month period is allowed for submitting comments or protests from the time of publication. Considering the *Chronicle* is in press some 2 months before issue and that the subcommittee will require time both before and after the 4-month waiting period, the minimum time needed for establishing a name will be about one year. Certainly no manufacturer will want to hold his product off the market for a year pending the WHO action in those countries of Europe and South America where each drug must bear an accepted nonproprietary name.

Proprietary names are generally three syllables in length, whereas it is rare for a nonproprietary name to be less than four syllables. In the case of 35 U.S.P. XIV drugs which are under patent control or exclusively marketed by a single firm under its trade name, the average syllable length of the U.S.P. title is 4.1, whereas the corresponding trade-marks average 3.2 syllables. In only one instance, Neo-Synephrine *vs.* phenylephrine, is the protected name the longer of the two.

The great emphasis placed on taking the nonproprietary name first put into use by the individual or firm developing a drug makes it obvious that the initial selection demands careful attention to the guiding principles of drug nomenclature established by the WHO. Those who have dealt with the A.M.A. Council on Pharmacy and Chemistry in the past will recognize most of them. They are set forth here in the interest of completeness:

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

General Principles for Guidance in Devising International Nonproprietary Names

1. Names should, preferably, be free from any anatomical, physiological, pathological, or therapeutic suggestion.

2. An attempt should first be made to form a name by the combination of syllables in such a way as to indicate the significant chemical groupings of the compound and/or its pharmacological classification. Preference should be given to the following syllables:

Latin	*English*	*Type of Compound*
-inum	-ine	For alkaloids and organic bases
-inum	-in	For glycerides and neutral principles
-olum	-ol	For alcohols and phenols (–OH group)
-alum	-al	For aldehydes
-onum	-one	For ketones and other substances containing the CO group
-enum	-ene	For unsaturated hydrocarbons
-anum	-ane	For saturated hydrocarbons
-cainum	-caine	For local anesthetics
-mer	-mer	For mercurial compounds
-sulfonum	-sulfone	For sulfone derivatives
-quinum	-quine	For antimalarial substances containing a quinoline group
-crinum	-crine	For antimalarial substances containing an acridine group
-sulfa	-sulfa	For derivatives of sulfanilamide
-dionum	-dione	For antiepileptics derived from oxazolidinedione
-toinum	-toin	For antiepileptics derived from hydantoin
-stigminum	-stigmine	For anticholinesterases

3. Names should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names already in use.

4. The addition of a terminal capital letter or number should be avoided as far as possible.

Chemists will recognize some ambiguity in Item 7, especially for those compounds which may be looked upon as falling into more than one group. Furthermore, the task of finding distinctive combinations of syllables having some relation to the chemical structure becomes more difficult year by year as the simple groupings are exhausted and the chemical nature of the drugs becomes so much more complex. The first tendency would be to take a path of least resistance and to choose names without regard to length and euphony. Two forces operate against this choice. First, there is the above-mentioned jeopardy to the protected trade-marked name if it is very much easier to use. Second, the movement among physicians and pharmacists to use the official names of drugs is gaining strength. As this movement picks up impetus, a greater and greater area becomes a fertile ground in which resentment against long, awkward names can sprout and flourish.

The chemist of the drug industry is in a strategic position to prevent this resentment by using judicious care in selecting nonproprietary names which will be wholly suitable for international use. Such efforts might be likened to using a preemergent weed-killing spray, which stops trouble before it gains headway.

Finally, there are bound to be cases when the nonproprietary name first proposed will not prove suitable internationally even though it has come into fairly general use in some one country. A prime example is the fact that the names of all of the chemical elements are not yet settled. When such cases arise it is to be hoped that all concerned will take an open-minded attitude conducive to working out a compromise in a spirit of true international cooperation.

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Current Medical Periodicals of Chemical Interest

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Tremendous increase of literature in the postwar years has heightened the difficulty of keeping abreast of printed reports. Therefore, it is important for chemists to know titles and sources of journals and bibliographic tools in which they are included. This paper surveys the field by furnishing this information, and discusses the influence on current periodical literature of chemical advances which affect medical research and clinical medicine.

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The qualifying phrase in the title might well have been omitted because practically every issue of most medical periodicals contains at least one such article. When that part of the title is eliminated, current medical periodicals remain, and the first question: "What is a medical periodical?" "One that deals with medicine" is the most obvious answer, but medicine is so intimately related to so many branches of science—bacteriology, psychology, physics, meteorology, and especially chemistry—that definite limits are not easy to determine. In medical library work, the *Journal of Bacteriology*, *The Journal of Comparative and Physiological Psychology*, and the *Journal of Biological Chemistry* are considered just as much a part of medical literature as *The American Journal of Medicine* or the *British Medical Journal*.

No general agreement on this point is indicated by various lists of so-called medical periodicals. The Indexing Research Project at the Welch Medical Library, Johns Hopkins University, prepared a list of 6369 serials on punch cards, of which a number cannot be classified as periodicals, and many are not strictly medical. United Nations Educational, Scientific and Cultural Organization has published *World Medical Periodicals*, which includes 4000 items and covers medicine, biology, pharmacy, odontology, and veterinary medicine. The fourth edition of *Periodica Medica*, printed by Georg Thieme Verlag, lists 12,624 titles which have been in print some time since 1900, and includes annual reports, congresses, bibliographies, and minor items of local character although it is claimed to be a selective compilation. Apparently there are no common criteria for such lists.

Publications Have Increased

Billings estimated 864 medical periodicals in 1880. The increase has been spread over the 70 intervening years, and has been almost alarming since World War II. Publishing in European countries, especially Germany and Italy, has made a remarkable recovery; some of the South American countries are especially prolific; the Japanese are producing a surprising number of periodicals; and the United States is not lagging behind.

Since 1950, the American Medical Association has maintained a card file of journals, new to its collection, which have been received from various sources. A check of those which began publication from January 1950 to date produced the following figures: 80 new titles in 1950, 73 in 1951, 66 in 1952, and 29 thus far in 1953. This represents only the journals received in this library and includes such widely divergent items as *Alam Attib* (World of Medicine) from Turkey, the *Bulletin of Mental Health* from the Virgin Islands, and the *Japanese Planned Parenthood Quarterly*, as well as journals of greater importance, such as *Acta Neurochirurgica*, *Antibiotics and Chemotherapy*, *Metabolism*, and the *Journal of Histochemistry and Cytochemistry*.

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During this period a few periodicals have ceased publication and some have been combined. An interesting record of these developments is furnished by the Medical Library Association's *Vital Notes on Medical Periodicals* which gives information on their births, deaths, and marriages.

Medical Publishers

Who publishes this wealth of material? First there are the medical publishing houses: C. V. Mosby & Co., W. B. Saunders Co., Charles C Thomas, Williams & Wilkins Co., and perhaps a dozen others in this country; Butterworth & Co., J. & A. Churchill, and H. K. Lewis & Co., in Great Britain; J. B. Balliere et Fils and Masson & Cie. in France; Einar Munksgaards Forlag in Denmark; L. Cappelli and Edizioni Minerva Medica in Italy; S. Karger and Benna Schwabe & Co. in Switzerland; and Springer-Verlag, Georg Thieme, and Urban & Schwarzenberg in Germany among many more. Next, there are the university presses and such organizations as the Wistar Institute of Anatomy and Biology and the Milbank Memorial Fund. A number of medical societies publish or sponsor their own periodicals. The American Medical Association is represented by the *Journal* and 9 specialty journals; the British Medical Association has 15 periodicals to its credit besides the *British Medical Journal*; the American Heart Association fosters *Circulation* and a new journal called *Circulation Research*; the American College of Surgeons is responsible for *Surgery, Gynecology, and Obstetrics* in addition to its *Bulletin*.

In fact, it seems that every hospital, clinic, and medical school in every country publishes a bulletin; every society has its own journal or at least prints its transactions; and most international congresses produce volumes of their proceedings. Some of these publications are limited to material, which will not appear elsewhere, but many of the articles are reprints, abbreviated reports, or a rehash of other papers by the authors. Others are of such minor importance that they merely clutter library shelves or waste baskets.

Periodical Literature

Another source of increase in periodical literature is the expanded bulk of individual journals in the last few years. In 1947 the volumes of the *J.A.M.A.* included 4242 pages; in 1952, 5 years later, 5152 or about 900 more pages. In the issues for May, June, and July 1947, 114 signed articles were printed, whereas in the corresponding period for 1952 this number was increased to 195, about 80 more for these three months, which probably means at least 300 more for the year. In this respect the *Journal* is typical of periodicals all over the world.

Much of this expansion probably can be attributed to the tremendous increase in research in recent years and what group is more responsible than the chemists and pharmacologists? A comparative count of articles in the May, June, and July issues of the *J.A.M.A.* for 1928 and 1953 verifies this impression. Of the 159 signed articles in 1928, 15% had chemical slant as shown by title; of the 190 signed articles in 1953, 36% were of chemical interest.

The author's experience with medical periodicals covers over 25 years of work on the *Quarterly Cumulative Index Medicus* (called *The Quarterly* by the staff and known to most persons as *Q.C.I.M.*) and most of this paper is based on this source of information. In one of the volumes of the *Q.C.I.M.* for 1928, the titles under "Diabetes Mellitus, insulin in" occupied a column, but the two substitutes, glukhormet (a vegetable product), and synthalin (a guanidine derivative), each required as much space. The "Suprarenal Extracts," as they were designated then, accounted for two pages, while in a 1951 volume, although the corresponding "Adrenal Preparations" took the same space, the additional "Adrenocortical Preparations" covered 9 pages and "Adrenocorticotropic Hormone" 7 more. In 1928 drug therapy of tuberculosis included insulin, calcium, an extract of walnut leaves, and a pine oil preparation, and even as late as 1948, a column of the index was devoted to gold therapy. Today, the literature is flooded with papers on streptomycin, *para*-aminosalicylic acid, thiosemicarbazone, and the latest recruits, isoniazid and its derivatives. Vitamins were designated A, B, C, D, and E before they became complex; the anterior pituitary was only suspected of such "tropism" as was later discovered; histamine was collecting its forces, but no one wrote about antihistamines. In fact, the main difficulty then was identifying the constituents of pro-

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prietary drugs, especially in the German literature; now they are fairly well controlled, and that whole problem seems insignificant in the fact of chemical substances grouped as anticonvulsant, adrenergic, sympathomimetic, spasmolytic, vasoconstrictor, anticoagulant, and carcinogenic, or the pesticides, the solvents, and other industrial products, to mention examples. In addition to proprietary names everyone is being confronted with a series of designations such as SN, SK, M&B, and RP combined with numbers that run into the thousands, chemical terms which can be written in several different ways, and the generic names of the manufacturer, the Council on Pharmacy and Chemistry, WHO, the British authorities, and any other interested parties. This all adds up to confusion which must be as harassing to the searcher as to the indexer.

When any new product or group of products is introduced, the first report printed in this country usually appears in the *Journal of the American Chemical Society* where the chemical make-up and properties are set forth. This announcement has scarcely been made before a crop of reports, first on animal experiments and then on administration to humans, both normal and sick, make their appearance. After this, if results are favorable, the field is open, the product is tried in every condition which it could conceivably affect, and medical journals receive the impact. At the height of this stage in the development of the sulfonamides, the cross references in the *Q.C.I.M.* from the subhead "therapy" listed almost 150 specific headings under which articles could be found, but in the last volume for 1951 there were only about one third that number. Therefore, a leveling-off process occurs as the value of a product is assessed. Simultaneously, reports on side reactions begin to filter in and sometimes reach proportions which definitely limit the application of a product or prohibit its further use. Both the therapeutic and toxic results stimulate a search for related compounds which may be more satisfactory, and endless derivatives, substituted compounds, homologs, analogs, and such are investigated with the results appearing in medical literature if they prove satisfactory enough to warrant trial.

To keep abreast of this accumulation of printed material the chemist has a wealth of literature in his own field which is generously abstracted and indexed in *Chemical Abstracts.* If he is interested in the clinical applications of his work, then the search of other sources is necessary. The two principal indexes to current medical literature are the *Quarterly Cumulative Index Medicus,* published by the American Medical Association, and the *Current List of Medical Literature* prepared by the Armed Forces Medical Library. The former unfortunately is behind schedule in production, but the latter is more up to date. Approximately one third of the periodicals covered is included in both indexes, an unfortunate duplication of time, effort, and expense, but otherwise they supplement each other. The chemical searcher may find direct references to his subject under headings in the *Q.C.I.M.,* while an indirect method of listing is used in the *Current List.* The register of articles in the latter arranges titles by publications; this should be a definite assistance to anyone desiring to follow the contents of any particular journal. Besides these general indexes there are those in special fields, among them *Cancer Current Literature,* published by the American Cancer Society, and national indexes, such as *Index Medicus Danicus,* covering the medical literature of one country.

The abstract publications are an excellent source of information. *Excerpta Medica,* printed in The Netherlands, appears monthly in 16 sections, each devoted to a special field and written in English, and covers literature from all over the world. Each volume of each section includes an index to its contents. The *Zentralblatter* of Springer-Verlag, which resumed publication after World War II, is valuable for anyone who reads German. The coverage of both publications is world wide, and combined they survey most branches of medicine. Also, a British journal, *Abstracts of World Medicine,* appears monthly but includes a relatively small number of periodicals, mostly well represented in other sources. Besides these, a number of abstracts journals deal with special subjects, such as *Industrial Hygiene Digest* prepared by the Industrial Hygiene Foundation; *Tuberculosis Index and Abstracts of Current Literature* issued in Great Britain by the National Association for Prevention of Tuberculosis; *Current Literature on Venereal Diseases,* a publication of the Public Health Service; and *Leukemia Abstracts* prepared by the John Crerar

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Library. In addition, various annual reviews, advances, yearbooks, and special bibliographies are produced by different organizations.

Of course, most important for current reference are the journals themselves. Out of 1900 journals received currently in the AMA library, about 1700 are boxed, and only about 1000 are included in the *Q.C.I.M.* The fact that *Chemical Abstracts* chooses articles from most of them indicates that they must be of interest to chemists. If a worker in this field feels it is advantageous to consult issues of such publications as they are printed, rather than to wait until they are indexed and abstracted, he can start by selecting medical titles from the list of abstracted journals in *Chemical Abstracts;* then for further suggestions, he can turn to the *Current List* and the *Q.C.I.M.* After this, if he wants to undertake an inclusive coverage, 4000 titles are available in *World Medical Periodicals* and the 12,000 in *Periodica Medica.*

If chemists are like physicians they tend to shy away from articles in foreign languages, but direct consultation of periodicals outside English-speaking countries is not to be disregarded. A visiting German doctor recently made the statement that some procedures reported in the United States as new had been known in Europe for a long time, and attributed the lack of information in this country to the fact that foreign literature is not read.

Suggestions for Periodicals

This seems to be an excellent opportunity to make certain suggestions regarding periodicals. The title of another paper on this symposium attracts the author's attention because it uses the phrase "fertility of medical literature." There is the root of the problem that confronts bibliographers, and for this reason thought might be given to contraception. Since, at present, it is apparent that it is almost impossible to exercise bibliographic control over scientific literature by indexes, abstract journals, and similar devices in any way that combines complete coverage with currency, it might be more practical to check its production.

Before a new periodical is launched, its actual value to scientific knowledge and research should be honestly assessed. One letter from an editor complained that he could not attract contributors because his journal was not indexed in the *Q.C.I.M.;* he did not seem to realize that authors felt no need for his publication as an outlet for their papers. A number of letters ask whether a certain prospective periodical will be included in the *Index* when it is still only a gleam in the progenitor's eye and long before the first issue has appeared. Eventually this attitude might lead to a stamp of approval in imitation of the AMA Councils, "Indexed in the *Q.C.I.M.*"

There are several ways in which the number of papers in any journal could be controlled. For instance, if a group of investigators has done a piece of work on some problem, is it necessary to split it up into four or five articles all published in the same issue of a periodical, or could it be printed as one report, which might not only save space in the journal, but also cut entries in an index and still give the paper ample coverage? Along the same line, must a separate report be made every time a different animal or a different drug is used in an investigation? This practice is especially characteristic of a French publication, and one reason why it was impractical to retain it on the list of periodicals indexed in the *Q.C.I.M.*

More discretion might be exercised in the selection of papers for publication. Is a short discussion which summarizes articles by other authors, but offers no critical material and nothing original, worth printing? Should another case report of a fairly common condition be published unless it adds something new to medical knowledge? In other words, should encouragement be given to the attitude toward publication which was criticized aptly by Bowers, University of Utah College of Medicine, at a recent meeting: "Don't get it right—just get it written"?

Certain features of the format make for speed in handling. The title, the volume, the number, and the date of each issue should appear either on the cover or on the first page where they can be quickly located, and not hidden in some inconspicuous spot among the advertisements.

The title of an article should preferably be brief, but it definitely should indicate its content. For example, hypothetically, when the use of a new product in peptic ulcer is reported, the title "Peptic Ulcer: Report of Case" is entirely inadequate; "New Treatment for Peptic Ulcer" is not much better; why not "Enterogastrone Therapy of Peptic Ulcer: Case Report" or some other phrasing that will give

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specific information? Even worse are the vague titles beginning "Random Thoughts on—" or "A Few Observations on—" and worst of all those made from quotations which may indicate the philosophical trend of the paper, but give no idea of the subject matter.

Nothing is more helpful to an indexer and also to a reader than a clear statement of its purpose at the beginning of an article and a summary at the end which outlines the main points discussed.

It is certainly assumed that any author has made some investigation of the literature before he writes on any subject. If a review article or another paper summarizes this material, it is not necessary to go over the whole process again. A gold medal to the writer who advises, "For a survey of the literature the reader may consult the recent article by Smith and Jones," giving the definite reference in a footnote, and then begins his own contribution.

In some of the best scientific publications, the use of initials for various preparations and procedures is becoming a common practice which may be an economy for the printer but an anathema for the reader. From long usage BMR, BCG, ECG, BP, CA, TB, and QCIM have become fairly familiar, but what are ECT, DMF, RPM, TABDT, TAT, and VDRL? How many can identify the following in your own field: DADPS, DHE-45, AMP, CTAB, TETMS, FHS, and INAH? In despair one uninformed but conscientious manuscript editor interpreted IBM as International Brother of Magicians because that was the only definition which could be found in the dictionary! Of course, the meaning of these initials is usually explained in the text, but where? If they must be used, a footnote on the first page should list them and their equivalents.

There probably are objections to these suggestions, which incidentally have been disregarded in the title of this paper and the use of the initials *J.A.M.A.* and *Q.C.I.M.*, but adopting them would improve medical and chemical periodicals for the reader as well as the indexer. At any rate it is hoped that those who write or edit may give them consideration. They are offered as the author's opinions and not those of her sponsor, the American Medical Association.

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Library Resources of the Pharmaceutical Industry

GERTRUDE BLOOMER

The Wm. S. Merrell Co., Cincinnati 15, Ohio

To meet the increasing information needs of management, and to make fullest use of the increasing amount of printed materials, pharmaceutical librarians have developed some special resources. These are described. Several services which are particularly helpful in the identication of pharmaceutical preparations are likewise mentioned. A high degree of cooperation among pharmaceutical librarians has facilitated the interchange of ideas and materials in this industry.

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The phenomenal growth of the pharmaceutical industry into a billion-dollar business has been both the cause and effect of the research which has been carried on not only in the industry's laboratories, but also in its libraries. In this highly competitive field where the miracle drug of today is supplanted next week by a still more miraculous drug, the use of current literature and the most up-to-date sources of information has become of prime importance. On the other hand, the volume of literature has increased to such an extent that it is a growing problem for the pharmaceutical librarian to keep up with the pace of publication and to filter out those items which are of greatest significance to the organization.

The most important asset of any library is, of course, its collection of books and journals. A basic list of books for a pharmaceutical library collection has been prepared by Lowe *(4)*. A list of journals would include the important chemical, medical, biological, and pharmacy titles, as well as a wide representation of journals in specialized and general science. Pharmaceutical librarians have developed some special resources to aid them in making the most of their book and journal collections.

One of the most outstanding of these resources is *Unlisted Drugs*, which is published monthly by the Pharmaceutical Section, Science-Technology Division, Special Libraries Association *(9)*. As its title indicates, this publication bridges the inevitable gap between the mention of a new drug in the literature or its appearance on the market, and its official inclusion in the drug encyclopedias, pharmacopoeias and formularies, and other sources of drug information. For each compound listed, *Unlisted Drugs* gives the composition, name of manufacturer, the purpose for which the drug is intended (that is, its action), the dosage (when this information is available), and at least one reference to the source of these data. *Unlisted Drugs* is the only known service which lists drugs systematically by their experimental numbers as soon as they are reported in scientific journals. If one wishes to find out some information about, for example, a compound which is known only as 278 R-255, *Unlisted Drugs* will disclose that the compound is 2-[*p*-chloro-α-(β-dimethylaminoethoxy)-α-methylbenzyl]pyridine hydrochloride, prepared by The Wm. S. Merrell Co., that its action is fungistatic, and that a discussion of the drug is to be found in *Journal of Investigative Dermatology*, vol. **20**, page 178 (March 1953).

Twenty-one pharmaceutical libraries in the United States, Canada, and Argentina cooperate voluntarily in this project, each library being assigned certain domestic and foreign journals which are scanned for new drugs. The required data are submitted once a month to the editor. On some items information is actually published in *Unlisted Drugs* in the same month in which mention of the compounds appears in the literature. In 1952, more than 2300 new pharmaceutical preparations

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE; Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

and experimental compounds were described in *Unlisted Drugs*. The list is indexed twice a year, the last index being cumulative.

In September 1952, the Pharmaceutical Section of Special Libraries Association published a *Union List of Periodicals in Pharmaceutical Libraries (8)*. This compilation lists the holdings of 25 pharmaceutical libraries in the United States and Canada. It locates the titles of some 1500 journals and government documents in the subject fields most closely related to pharmaceutical interests and also in the fields of business and manufacturing. The *Union List* is not only an aid to the librarian and research worker by serving as a guide to the journals found in most pharmaceutical libraries and, therefore, a guide to the journals regarded as most important to the industry, but it also points out sources for interlibrary loans. The directory of participating libraries and their librarians included in the *Union List* was revised in August 1953. The directory also supplies information as to which libraries will furnish photocopies.

The Committee on Pharmacomedical Nonserial Industrial Publications—known as *Copnip* among its sponsors—is another specialized source of information developed by the Pharmaceutical Section, Special Libraries Association *(1)*. A sample copy of this publication appeared in April 1953; volume 1, number 1 was published in September 1953, and later numbers have appeared quarterly. *Copnip* lists current, informational publications on drugs, diseases, and other topics of public health interest issued by manufacturers in the pharmaceutical and related industries, and by organizations supported by these manufacturers. These data are frequently valuable to pharmaceutical researchers, and difficult to find when needed. The list attempts to bring such material together in one place for the bibliographic help it offers. Serial publications, such as house organs and trade lists, and certain types of advertising material are excluded. This project likewise is on a cooperative basis, each librarian submitting to the editor certain specified data on all appropriate material put out by his own company, and on material put out by other companies when it is available.

Another project recently launched by the Pharmaceutical Section is *Drug Information Sources (2)*. This project supplements the list of national and international pharmacopoeias published in 1952 by Strieby and Spencer *(7)*. *Drug Information Sources* provides data on the drug encyclopedias, codexes, formularies, dispensatories, and related types of books, which have been published in various areas of the world since 1940. Material is obtained by exploration in large libraries, and by correspondence with individuals and institutions in many foreign countries. A particular object of this publication is the listing of books which present drugs under their proprietary or common names.

Still in the formative stage is a pharmaceutical abstracting service which it is hoped the Pharmaceutical Section will be able to publish. This service will provide abstracts covering a broad scope of subjects of interest to the industry, and do so at a low cost.

Aside from their obvious use to librarians who have interest in the pharmaceutical field and the many related fields, including chemistry and medicine, the most outstanding fact about the projects mentioned is their cooperative status. Each of them was launched and carried on by the voluntary cooperation of pharmaceutical librarians. There is no remuneration for any work done. Participants in *Unlisted Drugs* receive free copies of each issue; this is the only reward for the hours of work which go into the projects. It may be that such cooperative ventures are unique in the field of scientific research, at least in this country.

One of the sources of information on drugs already on the market is the *Modern Drug Encyclopedia*, published by Drug Publications, Inc. *(6)*. This directory of new pharmaceutical preparations and new dosage or use forms of older preparations is now in the 6th edition, 1955. It is kept reasonably up to date by a bimonthly supplement entitled *Modern Drugs*, which has a cumulative index in each issue. The Encyclopedia contains a "therapeutic index," which is a classified listing of types of medication and also diseases; a "generic name index," which lists the therapeutic agents accepted by the American Medical Association under their generic names; and a manufacturers' index which gives not only the names and addresses of the companies whose products are listed in the Encyclopedia, but also

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lists the products which are described in this particular edition. The supplemental *Modern Drugs* provides the same service for each issue.

Facts and Comparisons, edited by Kastrup, is another most useful tool in the pharmaceutical library *(3)* and supplies information on newer therapeutic agents so as to answer such questions as: What is it? What is it used for? Who makes it? Are there different sizes and strengths? Is it more or less potent than other like products? How does the price per dose compare with similar or like products? *Facts and Comparisons* is arranged in the form of tables, each table being given to one drug or type of drug combination. For example, the tables headed "nasal vasoconstrictors" include other tables listing antihistamine-containing solutions, antibiotic-containing solutions, sulfa-containing nasal vasoconstrictors, and aqueous nasal vasoconstrictor compounds. It is kept fairly well up to date by monthly replacement sheets, but not all tables are brought up to date every month, and as a result the publication cannot be expected to furnish the most up-to-date information on all new drugs.

No discussion of pharmaceutical library resources would be complete without mention and proper recognition of the *Merck Index (5)*. As it certainly must be for every librarian and research worker in the entire field of chemistry and widely related interests, the *Merck Index* is the pharmaceutical librarian's stand-by and right-hand help.

Some of the reference materials which pharmaceutical librarians have developed to serve the informational needs of their own organizations have been described. Mention has been made also of a few services which pharmaceutical librarians have borrowed from their fellow chemistry and pharmacy librarians. These sources represent some of the industry's librarians' efforts to cope with the ever-increasing mass of technical publications. Individual efforts, cooperatively exerted into larger projects, have resulted in some invaluable aids in serving the scientific research library and the workers and management who rely upon it.

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Indexing Methods as a Means of Increasing the Fertility Factor of Medical Literature

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Merck & Co., Inc., Rahway, N. J.

The assumption is made that the basic purpose of a system of cataloging or indexing of scientific literature in the field of pharmaceutical medicine is to make available a collection of data that will serve as a culture medium for the growth of scientific theory and lead to its fruition in the development of new methods of treatment and the discovery of new drugs. With this basic premise in mind, the practical aspects are presented, with emphasis on the employment and enlargement of the "Standard Nomenclature of Diseases and Operations" into a workable numerical index system specifically adapted to handle medical, pharmaceutical, pharmacologic, physiologic, and biochemical literature. Stress is placed on the practical aspects of such a numerical coding system, the use of the punch card and the mechanical sorter, and on the results that can be expected from the intelligent use of such a combination.

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The basic purpose of a system of cataloging or indexing scientific literature in the field of medicine is to make available a collection of data which may serve as a culture medium for the growth of scientific theory and its fruition in the development of new methods of treatment and the discovery of new therapeutic agents. It has been stated that ". . . the science of medicine is a collective endeavor progressing as a result of the ideas and observations of many men, and that on occasion significant ideas and observations rise from obscure quarters" *(3)*.

Obscure bits of data are important not only as isolated points of take-off into the uncharted field of new ideas and new areas for further exploration, but even more important is the correlation of related materials buried in the unwieldy mass of technical reports that the modern methods of printing and publishing have produced. It is no exaggeration to say that most of us feel, on occasion, that, in the search for the right answer to a scientific problem, we have been buried under an avalanche of technical data.

In a discussion *(1)* of the need for mechanized systems for literature searching, held recently at the Massachusetts Institute of Technology, attention was called to the magnitude of the problem. It was stated that the volume of technical information is growing at an exponential rate and that 20 years is about the average period of doubling. Scott, of the Interdepartmental Committee on Scientific Development of the U. S. Government, called attention to the fact that the expense of handling rises as the volume of information increases. In fact, there would seem to be danger of serious encroachment by literature-searching demands on the total man-hours available for research. Swedish investigators have estimated that literature searching accounts for about one third of the total cost of research. Either we must painfully dig our way out from under this staggering load by spending uncountable hours and large sums of money in sorting and evaluating or some means of escape must be devised in which mechanical aids can be enlisted.

The collection of periodicals and monographs that make up a medical library plus the files of personal communications and assorted written materials that make up the factual tools of research laboratories and technical industries such as the

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pharmaceutical industry, may be looked upon as a "collective memory" for all the work that has been done in this particular field. Part and parcel of "memory" as a concept is the ability to recall. The data must be classified in an orderly fashion so that any piece of the whole is easily and quickly accessible. Further it is not enough to be able to find a single fact. The data must be so arranged that all closely related facts are equally available. Then, in the event there is no exact answer, a choice of possible solutions is available.

There are a number of ways to build up and put in working order this "collective memory" of medical, pharmaceutical, pharmacological, chemical, and other related data but the solution that we have worked out serves our particular needs astonishingly well. Within a matter of hours, and frequently within a matter of minutes, a group of abstracts or all the available references in the current literature on a given subject can be obtained whether it is the mechanism of action of a given drug on a specific disease process or the currently used methods of treating a given type of dermatitis.

Specific, isolated, informational queries can be answered, bibliographic data can be supplied, clinical research data can be classified and correlated, collections of abstracts on any desired subject can be compiled for use in planning research, information can be located for the practicing physician who has a problem, and informational material can be made available to those engaged in advertising and selling the firm's products. All this can be accomplished by the integration of three working elements: punch cards and a mechanical sorter, a complex but understandable numerical code, and trained personnel.

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Punch Cards and the Mechanical Sorter

The punch cards and the mechanical sorter are at the same time the most spectacular and the least troubling of the three working elements. We use 27 vertical columns of twelve spaces each out of a possible eighty columns on the punch card. Vertical lines have been overprinted to divide the card into sections and headings suited to our particular needs have been inserted. The position and number of holes punched in the grid of spaces are determined by the coding numbers used in indexing the original data. Thus the card, after it has been punched, takes on individual characteristics which make it possible to feed an unsorted stack of cards into an electrical sorter which automatically distinguishes one group from all the others.

The Coding System

The coding system to be used with punch cards and the numerical sorter is, from the user's point of view, the most complex part of the entire problem. Numerical codes are, without question, the most concise and accurate means of indexing individual, isolated facts and, at the same time, groups of related data. It should be emphasized, however, that the system is only as good as the code. By and large, the system will stand or fall on the suitability and the adaptability of the numerical code chosen and on the accuracy with which the coding is done.

The importance of suitability is obvious. The need for flexibility is readily apparent, too, but it has more hidden dangers. Not only is the subject matter of science itself continually changing but the interests of the individuals using this "collective memory" of medical and related data are continually in a state of flux. Little specific advice can be given on how to achieve and maintain the flexibility of such a system other than to point out the need for it and to emphasize the importance of keeping it always in mind, not only by those who plan the numerical code (the numbers used must be as flexible as possible) but also by those who do the abstracting, indexing, and coding day by day. Simplicity and uniformity are also of great importance.

When the coding system now in use in the Medical Division of Merck & Co., Inc., was first planned, existing classifications of medical information were examined. The decision was made to use the "Standard Nomenclature of Diseases and Operations," published by the American Medical Association *(2)*, as the basis for the coding system. It should be pointed out that any already existing classification chosen as a foundation for a numerical code, designed to fit a specific but new need, will present problems of adaption. The essential thing is to choose a classification coming closest to the apparent needs.

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Standard Nomenclature. The "Standard Nomenclature" was worked out originally by a large group of individuals, insurance companies, and medical organizations, cooperating with the National Conference on Nomenclature and Disease, from 1928 until the first edition was published in 1932. Continual revision has been carried on and the fourth edition of the "Standard Nomenclature" appeared in 1952. It is primarily designed for the use of physicians, specialists, and hospital personnel, so that a uniform and standard terminology may be used in the recording of diagnoses. Thus, it was designed for its own specific job, and *not* intended to serve as a means of indexing data in clinical and experimental medicine, physiology, pharmacology, and the like. It is essential that hospital records be as uniform as possible if cases are to be available for study, review, and research, not only in each individual hospital but also on a nation-wide scale.

The following statement appears in the "Standard Nomenclature" (page 848):

Basically a medical nomenclature is a list or catalogue of approved terms for describing and recording clinical and pathological conditions. To serve its full function, it should be extensive, so that any pathological condition can be accurately recorded. As medical science advances, a nomenclature must expand to include new terms necessary to record new observations. Any morbid condition that can be specifically described will need a specific designation in a nomenclature.

It is further stated that

The purpose of the system of classifying disease employed in this book is to present a logical clinical nomenclature.
The "Standard Nomenclature" attempts to include every disease which is clinically recognizable and to avoid repetition and overlapping. . . . It has been designed primarily for use by clinicians, as the clinical diagnosis is a most important source of information on prevalence and distribution of the disease.

The problem of indexing of *informative* material has little in common with the problem of classification confronting the staff physicians and the medical record librarian in the average hospital. When the two problems are examined carefully it soon becomes apparent that the most surprising thing is that the system used for the hospital records can be adapted at all, much less used efficiently, for the indexing of physiological, pharmacological, and medical information. The explanation for the success of this adaption of the "Standard Nomenclature" to the indexing of informational medical material lies in the fact that the numerical code given in the "Standard Nomenclature" is built up of two components—the first refers to the part of the body affected and the second to the cause of the disease. These two main divisions themselves have innumerable components. As a result it is the tremendous number and possible combinations of items that render medical classification the overwhelmingly complex thing it is and yet make possible a logical classification.

Description of Numerical Code as Adapted for Use. The numerical code used in our indexing system is made up of five components:

A. Drug used (this section of the classification was devised by our personnel)
   1. Class of drug
   2. Specific drug
B. Route of administration (this section also was formulated by our personnel)
C. Diseases or disturbances (adapted from "Standard Nomenclature")
   1. Topography (where the disease process occurs)
   2. Etiology (causative factor)
D. Other identifications (formulated by our personnel)
   1. This is a miscellaneous group of unrelated designations such as "Experimental studies," "Metabolic studies," "Review articles," etc.
E. Drug effects (adapted from a section in "Standard Nomenclature" titled Supplementary Terms)

Coding for Drugs. Designating code numbers for drugs are made up of two parts, a group of two digits connected by a hyphen with a second group of three digits. The first two digits indicate the class of drug and the second group the individual drug.

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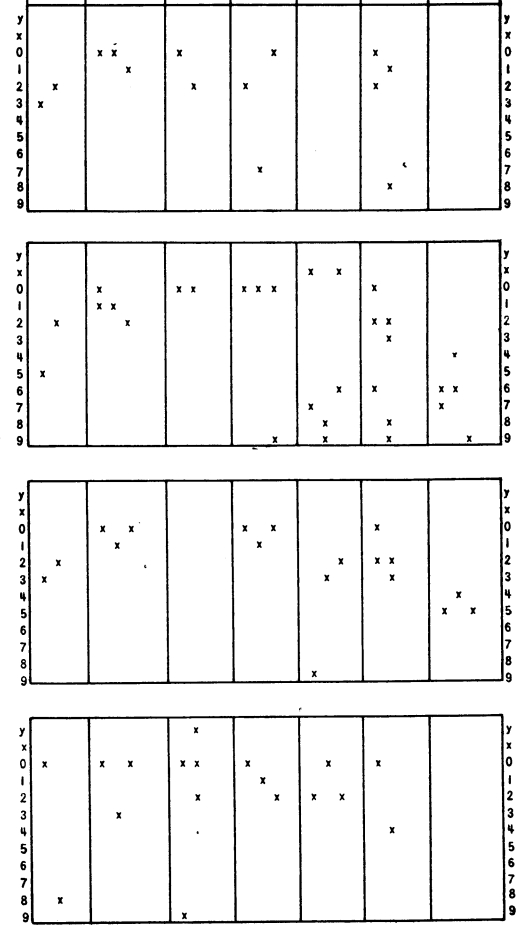
METHOD OF ASSIGNING NUMERICAL CODE DESIGNATIONS TO FACTUAL MATERIAL

SUBJECTS TO BE INDEXED	ASSIGNMENT OF CODE NUMBERS				
	DRUG	ADMINISTRATION	DISEASE	OTHER IDENTIFICATION	DRUG EFFECTS
Adrenal cortical extracts to improve muscle function in dogs. Mode of action is discussed	32-001 32 = hormones -001 = adrenal cortical hormone	02 = I.V.	270- = muscles (Note: in this instance the 1st 3 numbers of disease used to denote site of action of drug in experimental animals)	01 = animals 28 = mechanism of action	
Nicotinic acid orally in geriatric and senile patients: excretion studies - effect of acid and amide compared	52-012 52 = vitamins -012 = nicotinic acid 52-112 -112 = nicotinamide	00 = orally	000-x86 000 = psychobiologic unit, generally -x86 = adjustment reaction of late life 009-79x = chronic brain syndrome assoc. with senile brain disease 009 = nervous psychobiologic section -79x = senile dysfunction	02 = studies in man 29 = geriatrics 03 = pharmacol. (absorp., blood & tissue levels, excretion) 62 = comparison 28 = mechanism of action	749 = excretion in urine 669 = excretion in feces
Nitrogen balance in children receiving cortisone for rheumatic fever	32-010 32 = hormone -010 = cortisone		010-932 = rheumatic fever 010 = diseases affecting the body generally -932 = diseases in which the reaction is principally acutely inflammatory affecting a supporting structure predominantly	23 = children (up to 13th birthday) 02 = studies in man	545 = effect on nitrogen balance (original meaning - hyperproteinemia)
Terramycin in large doses, oral and intravenous, for Actinomycosis	08-030 08 = antibiotics -030 = terramycin	00 = orally 02 = I.V. 9y = large doses	012-202 = actinomycosis (012-2.. = mycosis, generalized) 012 = diseases secondarily affecting the body, generally -202 = actinomyces	04 = toxicity	

CODING ON THE PUNCH CARD
(EACH X INDICATES A HOLE PUNCHED IN THE CARD.)

MANNER IN WHICH CARD IS PUNCHED							
DRUG		ADMIN.	DISEASE		OTHER IDENT.	DRUG EFFECTS
CLASS	SPECIFIC		TOPOG.	ETIOL.		



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Actual examples are:

01–	Adrenolytic agents
02–	Amino acids
02–009	Histidine
03–	Elements
03–003	Calcium
04–	Analeptics
05–	Analgesics
05–005	Dromoran
06–	Anesthetics
07–	Anthelmintics
08–	Antibiotics
09–	Anticoagulants
09–001	Dicumarol
10–	Antiepileptics
11–	Antihistaminics
11–003	Antergan
11–006	Benadryl
28–	Diuretics
31–	Hematinics
52–	Vitamins
52–003	Ascorbic acid
52–009	Folic acid derivatives
–X00	A new drug that has been assigned no specific number
28–X00	Would, therefore, be a new drug that has a diuretic action

Coding to Indicate the Route of Administration of Drug. Since there is a comparatively small number of possible ways that any single drug can be given, this particular category requires only a small section of the punch card. It has been assigned two columns, each of which has twelve possible variations — x, y, and 0 to 9. The following are included:

0Y	Regimens (where emphasized)	10	Ocular
0X	Other than listed	12	Intraperitoneal
00	Oral	13	Cardiac
01	Intramuscular	14	Implantation
02	Intravenous	15	Intra-arterial
03	Subcutaneous	16	Intra-articular
04	Local	17	Intradermal
05	Inhalation	18	Intrapleural
06	Rectal	19	Intramedullary
07	Intraspinal	20	By stomach tube
08	Percutaneous		
09	Vaginal	6Y	Long term

Coding to Indicate Disease or Disturbance. This section of the coding is the most complex of all and, when purely clinical studies are indexed, is taken without change except for occasional shortening, from the "Standard Nomenclature." The number used is made up of two groups of digits. The first group of three indicates the location of the disease process (topography) and the second group of four indicates the causative factor (etiology). The first of the three digits which indicate the location, refers to the body as a whole or an organ system, the second and third digits refer to an organ or a part of an organ. There are ten main divisions:

0	Body as a whole (includes the psyche and the body generally)
1	Integumentary system
2	Musculoskeletal system
3	Respiratory system
4	Cardiovascular system
5	Hemic and lymphatic system
6	Digestive system
7	Urogenital system
8	Endocrine system
9	Nervous system
X	Organs of special sense

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Under the first section (or "System" as it is referred to in "Standard Nomenclature") there are the following subheads:

00 Psychobiologic unit
01 Body as a whole
02 Head and face
03 Neck, thorax, thoracic wall and mediastinum
04 Abdomen, abdominal wall and pelvis
05 Other areas of trunk
06 Peritoneum and serous sacs
07 Superficial fossae
08 Upper extremity — Subdivided further:
09 Lower extremity

080 Upper extremity, generally
081 Arm
082 Elbow
083 Forearm
084 Wrist
085 Hand, generally
086 Fingers, generally
089 Palm
08x Intrinsic vessels

The second group of four digits, which follows the hyphen in the compound number identifying the disease, indicates the causation of the disturbance. The main classifications are as follows:

0 Diseases due to prenatal influence
1 Diseases or infections due to a lower plant or animal parasite
2 Diseases or infections due to a higher plant or animal parasite
3 Diseases due to intoxication
4 Diseases due to trauma or physical agent
50 Diseases secondary to circulatory disturbance
55 Diseases secondary to disturbance of innervation or of psychic control
6 Diseases due to, or consisting of, static mechanical abnormality
7 Diseases due to disorder of metabolism, growth, or nutrition
8 New growths
9 Diseases due to unknown or uncertain cause with the structural reaction manifest; hereditary and familial diseases of this nature
x Diseases due to unknown or uncertain cause with the fuctional reaction alone manifest; hereditary and familial diseases of this nature
y Disease of undetermined cause

As a concrete example, diabetes mellitus would have the code number 871-785. Analyzing this number we find that

8 Refers to disease of the endocrine system
87 Refers to disease of the pancreas
871 Refers to disease of the tissue of the Islands of Langerhans
871-7 Refers to diseases due to metabolic disorders, growth, or nutrition
871-785 Refers to diabetes mellitus

Since the "Standard Nomenclature" was not designed to cover experimental and laboratory work, some provision had to be made to index such studies. The topographic section of the "Standard Nomenclature" number is retained if the idea to be indexed involves an effect on a certain part of the body, and the second part of the compound number is ignored. If, on the other hand, the important point is an effect on a body process, the second half of the compound number is used. The section on etiology of the "Standard Nomenclature" is searched for a number referring to the process involved. At this time the words "disturbed," "disturbance of," and "abnormal" in the "Standard Nomenclature" are disregarded.

According to our usage, a code number having a group of three digits connected by a hyphen to a second group of four digits is used for indexing purposes, when an article is concerned with patients or animals with a given disease. If only the first half of the number is used, the article is concerned with the effects of a drug on a certain section of the body; and if only the second half of the compound number is used, the effects of the drug on a certain body process or processes are discussed.

Coding Designated as Other Identifications. This category is used by our personnel to indicate a variety of unrelated matters, a miscellaneous group of odds

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and ends. Two columns of spaces are allowed for this assortment, examples of which include:

01 Experimental studies, other than man
02 Studies in man, experimental or clinical
03 Pharmacology (absorption, blood levels, excretion)
04 Toxicity
this column in conjunction with the three spaces in the last column (on "drug effects") indicate:
04; 000 No toxic effect
04; xxx Fatal
04; y.. Exacerbation of symptoms
04; ..y Precipitation of new symptoms
05 Contraindications
06 Bacteriology
07 Chemical and physical properties
08 History
09 Reviews and general articles
10 Nutrition
20 Assay
23 Children
24 Veterinary
29 Geriatrics
53 Antagonism of drugs

Coding of Drug Effects. This group of code numbers has been adapted from the "Standard Nomenclature." Originally it was intended to be used as a means of recording the symptoms of various diseases, but are used in our system to indicate the effects of a drug on the patient. This adaptation requires a certain amount of interpretation. For example, in an article on plasma volume extenders, one would not record "change in blood volume" after therapy (since that is the purpose of the preparation). However, if the patient developed a chill each time he received a plasma volume extender, this would be recorded. One instance so recorded might not be important, but several or many probably would have clinical significance.

In this category three vertical columns of digits are used. Samples of this code are as follows:

010 Dehydration
006 Gain in weight
008 Loss in weight
134 Petechiae
612 Anorexia
311 Dyspnea
206 Arthralgia

Additional Coding. In using the outlined system it has become desirable to indicate certain other characteristics. Fortunately, it was possible to adapt the system to include these. Different colored cards were used to indicate several broad categories. Brown punch cards, for example, are used for foreign references. This is important because, frequently, requests for information are from individuals living outside the United States. Since it is not only natural for someone in South America, for example, to read Spanish or Portuguese, but also easier for him to obtain such journals, an attempt is made to supply the inquirer with references to technical papers appearing in appropriate language journals.

Fortunately, since the cards were set up with eight vertical columns at the left of the punch card used only as space in which to write in code numbers, we were able to use one of these columns for foreign journals. Therefore, the proper digit in that column is punched so that cards referring to articles in a given language in periodicals from one country or group of countries, may be sorted mechanically. Thus the seventh vertical column on the cards is used as follows:

1 England
2 Germany
3 France
4 Spanish- and Portuguese-speaking countries, including South America
5 Oriental countries, including India
6 Italy
7 Holland, Belgium, Luxembourg, and the Scandinavian countries
8 The Near East
9 Russia
x Unrecognized
y Miscellaneous
0 Blank for future use

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The decision to leave one space in the column unused in keying the foreign references is an excellent example of the type of planning and of the attempt to foresee future happenings that are so essential to the lasting success of a system of this type. The need to plan ahead and leave a margin of safety cannot be overemphasized. Conditions change constantly and it is entirely possible that within the next five years some country, hitherto unimportant scientifically, may suddenly begin producing a sizable amount of technical literature. Under such conditions it would be highly convenient to have a means of keying those papers.

In addition to keying of foreign references, the left hand side of the card is used for other notations such as reference to abstract sections of journals.

Blue punch cards are used for articles not abstracted but indexed on punch cards only, white for articles from American or Canadian journals that have been abstracted and for which abstract cards are available, yellow for correspondence files, and so on. Columns five and eight have been used to indicate the year in which the report appeared and column 11 for the month.

How Technical Reports Are Coded

The first step in the process of indexing is to abstract the article. The abstracter writes the code number on the left-hand part of the punch card of the proper color. The sequence number of the abstract card is also written on the back of the punch card. At this time the last name of the first author and the literature reference are written on the bottom of the card beneath the last row of spaces. The punch card is then "mark-sensed." This mark-sensing merely means that the proper spaces on the right-hand side of the card corresponding to the code numbers are marked with carbon ink or pencil. The punch card is then ready to be fed into a machine which punches the holes in all spaces so marked. The card is then added to the already existing collection of punch cards ready to be sorted out by the mechanical sorter when a group of cards must be run to answer a specific question.

The actual assignment of code numbers to informational material can be best understood only by examining a specific example shown on page 58.

The numbers used for the preparation of the punch card for this particular abstract are indicated in the right margin. The letters in parentheses refer to the various sections or vertical columns in which the proper spaces are punched. The code numbers with their meanings are outlined below.

A. Drug used 23–003
- 23– Refers to the class..... carcinolytic agents
- –003 Refers to the specific drug within the class.. nitrogen mustard

B. Method of administration 02
In this case, intravenous injection

C. Diseases or disturbances 190–8191
(from "Standard Nomenclature") 783–8191
200–819.0
360–819.0

- 783– Refers to the cervex uteri (location or topography)
- 190– Refers to the breast
- 200– Refers to bones, generally
- 360– Refers to lungs, generally
- –8191 Refers to carcinoma (cause or etiology)
- –819.0 Refers to neoplasm with metastases
- 190–8191 Is therefore carcinoma of the breast
- 783–8191 Is therefore cervical carcinoma
- 200–819.0 Is therefore neoplasm with metastases to the bones
- 360–819.0 Is therefore neoplasm with metastases to the lungs

D. Other identifications 28
04

- 28 Refers to mechanism of action
- 04 Refers to toxicity

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E. Drug effects (adapted from the section "Supplementary Terms" in "Standard Nomenclature") ..... 006 008 5.. 611 612 614 y..

006 Refers to gain in weight
008 Refers to loss in weight
5.. Refers to the blood picture
611 Refers to nausea
612 Refers to loss of appetite
614 Refers to vomiting
y.. Refers to general deterioration of condition (not from "Standard Nomenclature")

Assignment of Code Numbers

Remold, F., and Siegert, A.: Use of nitrogen mustard → 23-003 (A)
in recurrent cervical and mammary carcinomas and in
metastatic tumors of bones and lungs, Ztschr. f.
Krebsforsch. 57:614 (abstract from the J.A.M.A., 149:206,
May 10, 1952).

"The aim of these studies was to ascertain the mode of
action → 28 (D)
and the therapeutic effect of nitrogen mustard → 783- (C)
in the treatment of recurrent cervical → 190 (C)
or mammary → -8191 (C)
carcinomas and of metastatic bone → 200- (C)
and pulmonary → -819.0 (C)
tumors. → 360- (C)

The following factors served as criteria: the patient's
subjective feeling; the objective status as determined
by palpation, auscultation and roentgen examination;
the general condition as manifested by body weight → 006 (E)
and → 008 (E)
blood picture → 5.. (E)
and finally the further course of the
disease. Particular attention was given to the blood
picture during and after treatment. The authors used
the 'tris' nitrogen mustard and, after commenting on
the different dosage schemes that have been used, they
say that they used Heilmayer's method, in which 0.05 mg.
per kilogram of body weight is administered every second
day. A total of 38 patients were treated. Secondary
effects in the form of malaise, nausea → 611 (E)
, loss of appetite → 612 (E)
, and vomiting → 614 (E)
as a rule were noted only after the third
or fifth injection → 02 (B)
. It was found that the treatment
with nitrogen mustard produced neither subjective nor
objective improvement, but rather a definite and
largely irreversible deterioration → y.. (E)
of the hematopoietic
function and impairment of the patient's general condition
with accelerated decline → 04 (D)
. The authors feel that treatment
with the nitrogen mustards is inadvisable and unjustified."

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Personnel

The personnel responsible for the day to day operation of this type of coding system must be vitally interested in the system itself and understand it not only in detail but from a broad point of view. It would be next to impossible to state how much output can be expected from a certain number of individuals for too much depends on the system itself, on the type of material indexed, and on the needs of the institution served by the system. At present we have four abstracter-coders, an abstracter's assistant, and a clerk-typist. Since this new system was inaugurated in April 1951, over 13,000 abstracts and 22,500 punch cards have been accumulated. Approximately 2500 journals will have been screened, abstracted, and indexed by this method during 1953.

The abstracter-coder must have a broad scientific education: some chemistry, some biology, some language, and as much premedical training as possible. In addition, at least one abstracter-coder should have a sense of numbers and experience with some type of numbering system. Scientific curiosity and a detective instinct are assets. An open mind and adaptability are musts. A personal interest in the system and a realization of its potentialities are fundamentally important as well as the possession of a creative attitude and ability to see the system as a whole. It is an absolute necessity that anyone who codes must be able to run the mechanical sorter and understand how it works in practice.

The abstracter's assistant can operate the mechanical sorter for answers to all but the most complicated questions. It is the assistant's job to check the punch cards for accuracy. In fact, accuracy is the most important qualification for this job. The clerk-typist, in addition to the usual type of work required, mark-senses the punch cards and is able to operate the mechanical sorter for answers to simple questions. Here again accuracy is required.

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What Are the Potentialities of Such a System?

How many individual items can be indexed on a punch card? The system used has twelve to the eightieth power, or a number corresponding roughly to the estimated number of electrons in the known universe. The limitations of this system are, therefore, the limitations of the human beings who devise the numerical code used and the individuals who do the indexing and coding.

How Does One Go About Setting Up Such a System?

The personnel trained in the subject matter to be indexed and the specialist in punch-card systems should cooperate in installing the system. Some system of nomenclature must be chosen and an estimate made of the number of categories of subject matter involved together with the approximate number of items within each category. Once the approximate scope of the coding is determined a punch card can be designed to suit the particular problem.

To illustrate, a hypothetical problem in indexing might be the following:

1. There are 60,000 ± 500 chemicals of a specific type (all containing the radical XO^-) and they can be subdivided into 50 ± 10 classes.
2. These chemicals are very likely to be insecticides and their effectiveness may be indicated by ++++, +++, ++, +, ±, and 0.
3. There are 20,000 species of insect (which can be separated into three groups—flying, crawling, hopping) native to 35 different countries.

The question then is—How many columns of twelve spaces each (x, y, 0 to 9) are necessary to put all possible combinations of this data on punch cards? Would hyphenated numbers be used? How would it look?

By simple arithmetic two vertical columns, of 12 spaces each, furnish 144 possibilities. Three columns furnish 1728, four columns 20,736, five columns 248,832, and six columns 2,985,984. Therefore, the punch card would probably need the following:

1. For the chemicals..... two columns for the class
   four columns for the specific chemical

   The code number would be of the 00–0000 type.

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2. For the effectiveness of the chemicals as insecticides only one column would be needed and the code numbers would be as follows:

0	++++
1	+++
2	++
3	+
4	±
5	0

3. For the insects one column is needed to indicate whether they were flying, crawling, or hopping, and four columns to indicate the species. Two other columns would more than suffice for the number of countries.

Therefore, the card would look like the following chart.

Chemicals									*The Insects*								
Class			*Specific*					*Effect*	*Type*	*Species*				*Country*			
y	y	–	y	y	y	y	y	y	y	y	y	y	y	y	y		
x	x	–	x	x	x	x	x	x	x	x	x	x	x	x	x		
0	0	–	0	0	0	0		0	0	0	0	0	0	0	0		
1	1	–	1	1	1	1		1	1	1	1	1	1	1	1		
2	2	–	2	2	2	2		2	2	2	2	2	2	2	2		
3	3	–	3	3	3	3		3	3	3	3	3	3	3	3		
4	4	–	4	4	4	4		4	4	4	4	4	4	4	4		
5	5	–	5	5	5	5		5	5	5	5	5	5	5	5		
6	6	–	6	6	6	6		6	6	6	6	6	6	6	6		
7	7	–	7	7	7	7		7	7	7	7	7	7	7	7		
8	8	–	8	8	8	8		8	8	8	8	8	8	8	8		
9	9	–	9	9	9	9		9	9	9	9	9	9	9	9		

Fourteen of the available vertical columns would thus be utilized. In this instance the x and y spaces are used as though they were numbers, i.e., no distinction is made. Ordinarily the x and y spaces are reserved for unusual designations. In our own system, for example, 08–x00 means a new antibiotic which has not been given a specific number. The reason for not assigning it a specific number might be that there was some question as to whether it might not be identical with another antibiotic already assigned a code number.

Filing of Punch Cards

The filing problem with punch cards varies according to the group using them. In this case, punch cards are filed in broad groups according to the classification number of the drugs involved. Obviously we have a tremendous number of references on such subjects as cortisone, penicillin, streptomycin, and antihistaminics. In answering specific questions it is time-saving to be able to pick up a group of cards likely to contain the answer for processing with the mechanical sorter. This mechanical sorter can handle 400 cards a minute. To date we have a total of 22,500 cards, some 4620 of which are on cortisone and hydrocortisone.

How Questions Are Answered

That the more specific the question the easier it is to obtain an answer is a maxim that must not be forgotten. The basic reason is inherent in the procedure necessary to get informational data out of the system into which it has been put. The process consists essentially of coding the question in the same manner that the data is coded, setting the sorter to pick out all the cards punched with the same code numbers as the question and then running the cards through the sorter.

Some typical questions which have been answered are:

Use of benzodioxane in the diagnosis and management of pheochromocytoma
Effect of cortisone on the mechanism of blood coagulation
Use of cortisone in sprue
Use of diamino diphenyl sulfone in leprosy and lupus erythematosus
Nalline, all references since January 1952

The first four of these are sufficiently specific to yield themselves to efficient and rapid handling. The last of the group, on the other hand, is of the type that can be very troublesome. In this particular case it does not present such a problem since there is not yet a large number of references on Nalline. If the question had been all the references on cortisone that have appeared since January 1952, it would

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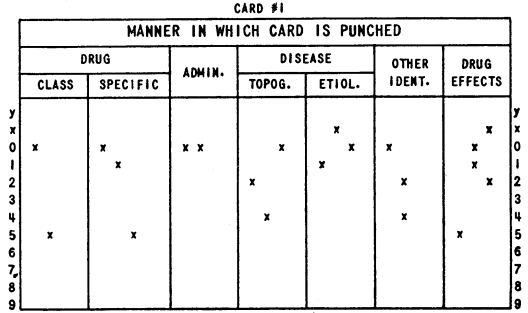
METHOD OF ASSIGNING NUMERICAL CODE DESIGNATIONS TO FACTUAL MATERIAL

SUBJECTS TO BE INDEXED	ASSIGNMENT OF CODE NUMBERS				
	DRUG	ADMINISTRATION	DISEASE	OTHER IDENTIFICATION	DRUG EFFECTS
Aminopyrine, for arthritis, causing agranulocytosis Treatment with cortisone and penicillin 3 punch cards used	05-015 05 = analgesics -015 = aminopyrine	00 = orally	240-1x0 = arthritis, rheumatoid, multiple 240 = joints -1x0 = generally and unspecified; localized inflammatory lesion; chronic inflammation; inflammation due to remote infection	04 = toxicity 02 = studies in man	512 = "granulocytopenia" 50x = leukopenia
	32-010 32 = hormones -010 = cortisone	01 = I.M.	502-3452 502-300 = agranulocytosis due to intoxication or drug reaction 502 = granulocytic tissue (myeloid) -3452 = diseases due to intoxication, aminopyrine	02 = studies in man	
	08-022 08 = antibiotics -022 = penicillin		y00-100 y00 = topography unknown -100 = disease due to general or unspecified infection	02 = studies in man 14 = prophylaxis	

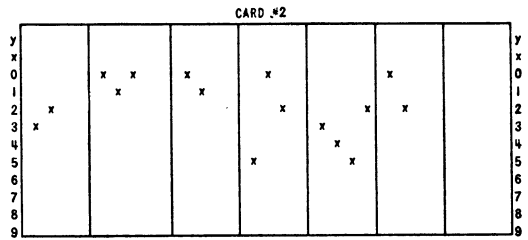
CODING ON THE PUNCH CARD

(EACH X INDICATES A HOLE PUNCHED IN THE CARD.)

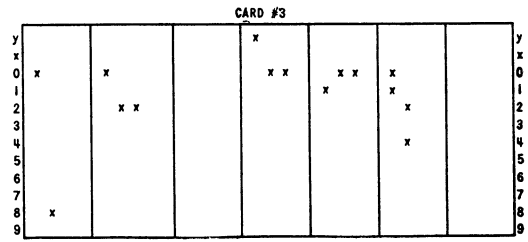
CARD #1



CARD #2



CARD #3



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have presented quite a different problem. The tremendous number of references forthcoming would have been overwhelming and unwieldy even if the individual who asked the question intended to do no more than have these references typed in the form of a bibliography.

What Is Accomplished by Use of Punch Card and Mechanical Sorter?

The use of the punch card and the mechanical sorter by trained personnel who have been provided with a workable numerical coding system is the most efficient and the most effective practical method we have found to increase the fertility factor of scientific literature or, more specifically, medical literature. At first glance some might think it unnecessarily complex, others might fear it to be expensive. But on closer examination it quickly becomes apparent that no indexing system commonly used can produce a comparable amount or extent of information in relation to the labor, time, and money invested. For example, the title of an article, *The use of cortisone and penicillin in the treatment of agranulocytosis caused by the use of aminopyrine in treating a patient with arthritis,* is by no means unique in length or in the number of items that should be noted if the article is to be properly absorbed into the "collective memory" of medical and pharmacotherapeutic literature. The conventional type of card file index would probably include the following separate cards:

1. Master card giving complete reference (authors, periodical name, volume, page, date) and probably abstract
2. Author card (this may be a duplicate of card 1)
3. Card with the heading *Cortisone* and referring to card #1
4. Card with the heading *Agranulocytosis* and referring to card #1
5. Card with the heading *Aminopyrine* and referring to card #1
6. Card with the heading *Arthritis* and referring to card #1
7. Card with the heading *Penicillin* and referring to card #1

Under our adaptation of the punch card system, there would be the following:

1. The same as the master card (#1) above
2. Same type of author card (#2)
3. A punch card coded to indicate
   Aminopyrine, analgesic, given orally to a patient with rheumatoid arthritis, had a toxic effect, causing agranulocytosis
4. A punch card coded to indicate
   Cortisone, a hormone given orally, to treat agranulocytosis in a patient who had developed this condition as a result of receiving aminopyrine
5. A punch card coded to indicate
   Penicillin, an antibiotic, administered, in order to prevent infection

The original report is more completely indexed on the five cards used in the second system than by the seven cards of the first. The more complete the index the easier it is to locate isolated facts. With the nonpunch card system, all seven cards must be filed alphabetically in their proper place and many running feet of card file drawers must be manually handled and visually scanned to locate material.

In the second system, the first two are filed in a similar fashion. The master card is given a number and filed by consecutive number, the second card is filed alphabetically by the last name of the sole author or of the first author listed in a series. The three punch cards (which also carry on the reverse the number of the master card) are simply placed in the three filing sections labeled analgesics, hormones, and antibiotics. If a question arises concerning the toxic effects of aminopyrine in the treatment of arthritis, one need only set the mechanical sorter to select all the cards carrying references to this, insert the stack of cards from the section on analgesics and await results. Assuming that there may be 1500 punch cards on analgesics, it will take less than five minutes for the machine to find the information *accurately.* By comparison, a human being under the old system might have needed hours to search through a large number of cards.

Once the punch card, or cards, indexing the desired data, have been selected by the mechanical sorter, only a note of the number written on the back of the punch card needs to be made if one wishes to locate the abstract in the master file, or to note the reference written on the punch card if the circumstances are such that it seems desirable to consult the original article directly. The punch cards, having served their immediate purpose, are then returned as a group to the drawer—a

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much more time-saving process than laboriously refiling individual cards in specific locations. In addition to being more rapid, the system is far more accurate and practically eliminates lost and misplaced (misfiled) index cards.

Some indication of the efficiency of this system is that the staff can scan, abstract, code and prepare punch cards for pertinent technical data in at least two hundred separate journals per month. Besides the routine filing away of many hundreds of resulting abstracts answers are supplied regularly in the form of abstracts and reference lists to between seventy-five and a hundred questions per month. A weekly publication is prepared of the 20–25% of the abstracts deemed of most timely interest to the company personnel. At the present time (1953), our "collective memory" of data-bearing punch cards is growing at the rate of about 1500 cards per month.

Literature Cited

(1) *Chem. Eng. News*, **30**, 2806–10 (1952).
(2) Plunkett, R. J., and Hayden, A. C., "Standard Nomenclature of Diseases and Operations," 4th ed., Blakiston, Philadelphia, Pa., 1952.
(3) Rogers, F. B., The Armed Forces Medical Library, *Military Surgeon*, **112**, 246–9 (April 1953).

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Literature Sources of Mammalian Toxicity Data, with Special Emphasis on Tabulating Machinery Applications

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A Chemical Toxicity Registry has been developed for the purpose of cataloging and reproducing mammalian toxicity data at low cost with standard punched card tabulating equipment. This report summarizes:

1. **A survey of the literature sources, and a method for coding the references.**
2. **A concise method for coding, tabulating, and correlating the toxicity data.**
3. **A simple method for linearly describing the corresponding structures of the chemicals with the 37 "teletype" symbols of standard tabulating equipment.**
4. **A simple method for sorting functional groups in an elementary manner.**
5. **A decimal method for coding the formula index and ring index values according to five natural numeric measures.**
6. **A simple method for supplementing the above chemical identifications with a short name or coded systematic name, based on established word roots.**

When the industrial hygienist is asked what type of health protection should be provided in some exposure to a new chemical, determination must be made as to whether the chemical is dangerously toxic or only slightly toxic. Thus, in both the industrial and medical fields, biochemical toxicity data are as important as the physical chemical data on vapor pressures, transition temperatures, solubilities, and reactivities. In answering such questions, the hygienist usually turns to the literature to find what has been reported about the health hazard. Unfortunately, data of this type recorded in the literature must be used with care because no standardized method or basis for reporting data exists.

Consequently, much must be done in the standardization and distribution of this fundamental information. In 1953, *Chemical and Engineering News (2)* announced a commendable new National Safety Council program to evaluate the handling and shipping hazards of new chemicals with a minimum of five standardized toxicity tests. Standardization also is needed for the efficient storage and retrieval of all kinds of data relating to specific chemicals. Indexing is becoming mechanized *(3)*, but the abstracting and cataloging cost is so great that the task cannot be attempted unless the information is shared through pooled research efforts *(10, 13)*.

The author is convinced that satisfactory standardization can be achieved in the immediate future if the problem is given the proper scientific attention. Early in 1953, a simple "checkoff" questionnaire was sent to a number of pharmaceutical and toxicological laboratories, in a systematic effort to obtain majority opinions from these authorities on four basic questions:

1. Which journals are most widely regarded as literature sources containing —or leading to—mammalian toxicity information? (answered in Table I).

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2. Which specific toxicity measures are most widely favored as standards? (answered in Table II).
3. Which of the many kinds of structure measures seem most promising for classification and correlation purposes? (answered in Table III).
4. Which types of concise identifications for chemical compounds are favored in systematic toxicity tabulations? (answered in Table IV).

For many years the author has been interested in locating, recording, storing, retrieving, and correlating toxicity data through the use of systematic measures and mechanical aids. The present paper describes a system employing punched cards adapted for visual and mechanical manipulation, which has been developed as the result of many experimental refinements. In this system three main series or decks of cards are prepared:

1. "Chemical identification" cards (one for each compound) on which are recorded:
   - *a.* The chemical structure, written in the Wiswesser notation,
   - *b.* A short name identification,
   - *c.* Biochemical and physical data,
   - *d.* The functional groups present in the compound,
   - *e.* A "formula file number" based on the compound's empirical formula, and
   - *f.* The literature reference in terms of year of publication, author, and journal. If more than one reference is recorded, additional cards are provided on which items *b*, *c*, and *d* are replaced by as many as eight year-author-journal references.
2. "Reference identification" cards (one for each reference) on which are recorded:
   - *a.* Name of author(s),
   - *b.* Abbreviated title or subject, and
   - *c.* The literature source in terms of journal, year, volume, page, and author's initials. The year-author-journal marks permit correlation of a specific reference card with one or more "chemical identification" cards.
3. "Journal identification" cards (one for each journal) on which are recorded:
   - *a.* The title of the journal, book, or other literature source,
   - *b.* The address of the publication, in terms of city, zone, and state (or country if not United States), and
   - *c.* A two-letter code to indicate the literature source. This code permits correlation by machine with the described "reference identification" and "chemical identification" cards.

Ordinarily, searches in terms of chemical structure, property, or name are conducted on the "chemical identification" cards. When the desired cards have been located, the appropriate "reference identification" and "journal identification" cards are selected mechanically, making use of the common code. In case the number of selected cards is large, the three types of cards are correlated and sequenced—also by high-speed machine methods.

The information sought may be taken manually directly from the cards, or the cards may be fed into a tabulating machine to list the information in any preferred arrangement (at the rate of 9000 cards or complete lines of information per hour). If multiple copies are desired, these can be run from Ditto masters made at the same rate in the tabulating machine, with Ditto tabulator carbon.

The layout of these cards, the technique of recording or searching, and other comprehensive uses of these cards are described in subsequent sections of this paper.

Toxicity Literature

Current sources of toxicity data (periodicals) are listed in Table I, which includes the suggestions and revisions obtained through the author's questionnaire. In this list, the current sources are arranged and identified by means of a two-letter code, referred to hereafter as the J-Code—i.e., Journal Code.

Mailing addresses and other detailed information on these sources were obtained from a comprehensive current list *(8)*, prepared in 1953 by the Industrial Hygiene Foundation, at the Mellon Institute. The abbreviations used in that list "conform, with some modifications, to those used by *Chemical Abstracts*," and the list is arranged in the alphabetic order of the abbreviations. This same arrangement is followed in other comprehensive lists *(11)*, so this majority preference

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also is followed in Table I. For example, the abbreviated letters in *Ind. Hyg. Digest* come before *Index Medicus*, even though the represented word "Industrial" would follow "Index."

Table I. Current Sources of Toxicity Data[a] (Illustrating the Two-Letter J-Code)

AA	Acta Med. Scand.	IY	Can. J. Comp. Med.	QY	J. Pharm. Ex. Thp.
AE	Acta Pharml. Tox.	JB	Can. J. Med. Sci.	RB	J. Physiology
AI	Acta Physio. Scn.	JF	Can. J. Res. (Tec.)	RF	J. Sci. Food Agr.
AM	Acta Radiol.	JJ	CAN. MED. ASSN. J.	RJ	J. Urology
AQ	Agr. Chemicals	JN	CANCER RESEARCH	RN	Klin. Wochschr.
AU	Agr. & Food Chms.	JR	CHEM. ABSTRACTS	RR	LANCET
AY	Am. Heart J.	JV	Chemical Age	RV	Med. Bul. SO/NJ
BB	Am. Ind. Hy. An. Qt.	KC	Chem. Engg.	SC	Med. J. Australia
BF	Am. J. Clin. Path.	KG	Chem. Eng. News	SG	Med. Klinik
BJ	Am. J. Dis. Chldrn.	KK	Chem. Products	SK	Med. lavoro
BN	Am. J. Medicine	KO	Chem. Safety D.	SO	Med. Res. Lab. Rep.
BR	Am. J. Med. Sci.	KS	Chem. Trade J.	SS	Mfg. Chemist
BV	Am. J. Obst. Gync.	KW	Chemisch. Zentr.	SW	Minerva Medica
CC	Am. J. Ophthalmol.	KZ	Chemistry & Ind.	SZ	Minnesota Med.
CG	AM. J. PATHOL-OGY	LD	Circulation	TD	Modern Sanitn.
CK	Am. J. Pharmacy	LH	Circ. Research	TH	Monthly Rev. N. Y.
CO	Am. J. Physiology	LL	Compens. Med.	TL	Nat. Nuc. En. Ser.
CS	Am. J. Pub. Health	LP	COMPT. REND.	TP	Nat. Safety News
CW	Am. J. Roent. Ra. T.	LT	Com. ren. soc. bio.	TT	Nature
CZ	Am. J. Trop. Med. H.	LX	Cornell Vet.	TX	NEW ENG. J. MED.
DD	Am. J. Vetnry. Res.	MA	CURRENT LIST M.	UA	N. Y. State J. Med.
DH	Am. Rev. Tuberc.	ME	Curr. Med. Digest	UE	Nord. Hyg. Tidskr.
DL	Anat. Record	MI	Deut. med. Wochsr.	UI	Nucl. Sci. Absts.
DP	Angiology	MM	Diseases of Chst	UM	Occpl. Health
DT	ANN. INTERN. MED.	MQ	Endocrinology	UQ	Ohio Ind. Com. Mr.
DX	Ann. pharm. franc.	MU	EXCERPTA MEDICA	UU	Ohio St. Med. J.
EA	Antibio. & Chemo.	MY	Exptl. Cell Res.	UY	Pa. Bur. Ind. Hyg.
EE	Arch. Bioch. Biop.	NB	Federatn. Proc.	VB	Perfumer
EI	Arch. Derm. Syph.	NF	Folia Haematol.	VF	Pest Control
EM	Arch. Ex. Path. Ph.	NJ	Folia medica	VJ	Pharmcl. Revs.
EQ	Arch. f. ges. Phys.	NN	G. Brit. H. M. S. O.	VN	Physics Today
EU	ARCH. IND. H. O. M.	NR	Gigiena i Sanit.	VR	Practitioner
EY	Arch. Intern. Med.	NV	Helv. Med. Acta	VV	Pr. Am. Vet. Md. An.
FB	Arch. int. pharmd.	OC	Ind. Eng. Chem.	WC	Pr. Soc. Ex. Bi. Md.
FF	Arch. int. physio.	OG	Ind. Health B. NJ	WG	Pr. Soc. St. In. Md.
FJ	Arch. mal. profes.	OK	Ind. Health Mo.	WK	PUB. HEALTH REPS.
FN	Arch. Pathology	OO	Ind. Health Rev.	WO	QRT. J. EX. PHYSIO.
FR	Assn F&D Offls.	OS	IND. HYG. DIGEST	WS	Rev. Tuberculose
FV	Atomic En. Comm.	OW	IND. MED. & SURG.	WW	Sammlung. Vergft.
GC	Biochim. biophys.	OZ	Ind. Data Sheets	WZ	Schweiz. med. Wo.
GG	Biochem. J	PD	INDEX MEDICUS	XD	Science
GK	Biochem. Zeit.	PH	J. Allergy	XH	Semaine hop. Paris
GO	BIOL. ABSTRACTS	PL	J. AM. MED. ASSN.	XL	So. Afr. Med. J.
GS	Blood	PP	J. AM. PHARM. ASN.	XP	Soap Sanit. Chem.
GW	Bol. soc. it. bio.	PT	J. AM. VET. MD. AN.	XT	Southern Med. J.
GZ	BRIT. ABSTRACTS	PX	J. BIOL. CHEM.	XX	Squibb Abs. Bull.
HD	Brit. J. Cancer	QA	J. Gen. Physiol.	YA	SUMMARY TAB., NRC
HH	Br. J. Exp. Path.	QE	J. Hygiene	YE	Tex. Rep. Biol. Med.
HL	BRIT. J. IND. MED.	QI	J. Lab. Clin. Med.	YI	Tr. Asn. Ind. Med. O.
HP	Brit. J. Nutritn.	QM	J. Nutrition	YM	Trans. Nat. TB Asn.
HT	BRIT. J. PHARMCL.	QQ	J. PATH. BACTL.	YQ	U. S. Armed F. M. J.
HX	Brit. J. Ven. Dis.	QU	J. PHARMACY & P.	YU	U. Cal. Pb. Pharm.
IA	Brit. Med. Bul.			YY	Wien. Klin. Woch.
IE	BRIT. MED. J.			ZC	Z. ges. in. Med. G.
II	Bull. Hygiene			ZG	Z. physiol. Chem.
IM	Bul. Johns Hp. H.			ZK	Z. Unfallmed. Bk.
IQ	Bul. mem. soc. md.			ZO	Zent. Arbeitsmed.
IU	Bull. Soc. chim. F.			ZS	Zent. f. Chir.

[a] Names of most widely consulted journal or abstract sources are capitalized.

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Journal Identification Cards. The full titles and mailing addresses of the sources listed in Table I are best elaborated on a master set of just a few hundred "journal identification" cards. These have a layout as suggested in the examples below; a separate card is used to record the data on each horizontal line, such as the "title line" itself. Each mark, space, or dot represents one of the 80 columns available on the IBM information-carrying cards. The blank spaces here denote printing spaces (on the cards and in tabulations) that do not require corresponding separating blanks in the punched columns of the cards—for example, between columns 43 and 44, or between columns 49 and 50. Punched column recording capacity is never wasted to separate the printing of adjacent fields. Thus, successive lines of information—i.e., cards—appear as follows, when sorted by the J-code in columns 48 and 49.

```
COLUMN  1         2         3         4         5         6         7         8
12345678901234567890123456789012345678901234 45 67 89 012345678901234567890123456789
.TITLE OF PERIODICAL IN 40 OR LESS MARKS.V. Y. A. J. CITY AND ZONE SYMBOL..STATE...#
ACTA MEDICA SCANDINAVICA..... .. .. AA STOCKHOLM K.....SWEDEN....
ACTA PHARMACOLOGICA ET TOXICOLOGICA..... .. .. AE COPENHAGEN K.....DENMARK...
AGRICULTURAL CHEMICALS.....INDUSTRY PUBLNS .. .. AQ NEW YORK 1.....NEW YORK..
AMERICAN INDUSTRIAL HYGIENE ASSN QUARTERLY. .. .. BB CHICAGO 11.....ILLINOIS..
AMERICAN J OF CLINICAL PATHOLOGY..... .. .. BF BALTIMORE 2.....MARYLAND..
ANNALS OF WESTERN MEDICINE AND SURGERY..... .. .. DZ LOS ANGELES 5.....CALIFORNIA
ARCHIVES BELGES DE MED SOCIALE HYG ETC..... .. .. EC BRUSSELS.....BELGIUM...
ARCHIVES OF INDUSTRIAL HYGN AND OCCPL MED.2 50... EU CHICAGO 10.....ILLINOIS..
J OF INDUSTRIAL HYGIENE AND TOXICOLOGY...31 49 .. Q2 ..SEE 50 EU.....
```

The title of the periodical, as shown by the leading card, is given in the first 40 columns; this field size is sufficient to permit the vast majority of names to be spelled out in full. A few obvious abbreviations like "AMER" and "J" are justified by their extensive usage. The journal code from Table I is punched in columns 48 and 49 (in the "J" space). The source address is confined to a 20-column "city and zone" field (columns 50 through 69) and a 10-column "state or nation" field (columns 70 through 79); the information punched into these last 30 columns is printed most conveniently (by the IBM "interpreter") on the second printing line of these journal identification cards. (Standard IBM tabulators also can be wired to list two-line sets in a similar manner, with columns 44 through 49 also on the second line.)

New titles are added with reserve letter combinations such as DZ and EC in the above list of examples; and old titles no longer in use can be included as letter-number combinations, such as the Q2 example.

Optional volume-year correlations are shown in columns 41 through 45 on these cards. For example, the printed figures can show the number of volumes per year and the first year of publication of a new journal—as in the EU example —or the last volume number and last year of publication of a discontinued one —as in the Q2.

The last column 80 (#) is reserved to distinguish the different decks or sets of cards—e.g., the journal identification, reference identification, or chemical identification cards—and the succession of additional cards (first, second, or third) when more than one is necessary to record the full information. In most cases more than enough space is provided on a single card, and this reserve capacity can be used for supplementary information. For example, the 40-column field for the journal name is sufficient to show the following helpful detail:

OCCUPATIONAL HEALTH..U S GOVT PRINTG OFC

This principle of providing economic use for reserve capacity also is illustrated in the "reference identification" and "chemical identification" cards.

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Reference Identification Cards. A few hundred cards suffice to identify the journal and text sources of toxicity data, but references to specific articles may run into the thousands in a master catalog. Hence all of the literature source information is made available for many kinds of punched card correlations (by journal, date, author, subject, etc.) through the inclusion of a distinct set of "reference identification" cards.

Specific journal articles are identified on these cards, with authors' names, page-volume numbers, the year-author-journal codes, and short title or subject identifications (see preceding comments on journal identification cards):

```
COLUMN  1         2         3         4         5         6         7         8
12345678901234567890123456789012345678901234 45 67 89 01234567890123456789012345678901
.LAST NAMES AND INITIALS OF AUTHORS.PAGE..V Y. A. J. TITLE OR SUBJECT IDENTIFICATN.#
BRANDT A D...MC CONNELL AND FLINN..00132.61 46 AB WK COMPOSN OF TRADE NAME SOLVENTS
COOK WARREN A.....00936..7 45 WC OW SUMMARY OF M A C VALUES.....
LEHMAN A J...CHEMICALS IN FOODS....00047.16 52 AL FR SUBACUTE AND CHRONIC TOXICITIE
LEHMAN A J...CHEMICALS IN FOODS....00122.15 51 AL FR PESTICIDES AND TOXICITIES.....
MC CORMICK WM E.....00038.13 52 WM BB CHEMICALS IN RUBBER PRODUCTS..
MC LAUGHLIN R S..500 CASE REPORTS..01355.29 46 HM CC EYE BURN CASES FROM 180 CHMLS.
SLOAN KETTERING INST FR CANCER RES.00376..4 52 SK YA INTRAPERIT TOLERANCES FOR MICE
SMYTH H F JR AND C P CARPENTER.....01363.29 46 HS CC EYE INJURY GRADES ON 180 CHMLS
```

The first 35 columns of these reference cards are reserved as shown for author (and subtitle, etc.) information, and the last 30 (columns 50 through 79) for subject identification. The latter information is printed (interpreted) on the second printing line of these cards, as with the journal identification cards. More elaborate subject coding could be used if some of the "title" columns were reserved for that purpose, but the self-evident word descriptions seem to be preferred in these cards.

Five columns (36 through 40) are reserved for the page number, and the next three (41 through 43) for the volume number. Here again the blank spaces in the leading card denote *printing* spaces that separate adjacent punching columns.

Each specific journal reference is identified by a unique six-column code (columns 44 through 49), composed of three pairs of symbols: two digits which directly identify the year number, two letters which generally give the author's initials, and the two "journal code" letters from Table I.

Text and pamphlet references also can be included in this six-column code. *Books* are distinguished by a blank space in the fifth position (column 48), followed by the publisher's initial in the last position. Miscellaneous *pamphlets* are distinguished by a blank space in the third position (column 46), followed by a three-letter identification of the issuing organization; such as ACS, NSC, NRC, PHS, SPB etc. These three-letter organizational identifications can be elaborated on "journal identification" cards.

Chemical Identification Cards. A widely applicable third set of cards complements the above two sets by summarizing the tabulated physico-biochemical data for each specific compound. If the information on a chemical card is summarized in a single reference, the corresponding reference code is given in columns 44 through 49, exactly as described above. Otherwise, a multiplicity of reference code numbers is given on a chemical card having "R card" printed in the reference field (columns 44 through 49). One such "R card" can carry up to eight reference codes (for a simple chemical structure) in addition to the complete chemical notation and a formula-ring-indexing "serial number" identification (see "Formula Index Numbers"). This multi-reference layout for a chemical card is illustrated below, with others.

The chemical card layout is illustrated below, in terms of the field identifica-

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tions for structures with increasing degrees of complexity (increasing length of notation). The 80 consecutive punching columns are identified across the top by adjacent numerals, without the printing (interpreting) spaces that are provided after columns 43, 45, 47, and 49. As in the preceding two sets of journal and reference cards, the printable information in the first 49 columns is "wired" to be printed across the top printing line of the card; the remaining printable information appears on the second line.

```
COLUMN   1         2         3         4              5         6         7         8
12345678901234567890123456789012345678901234 45 67 89 01234567890123456789012345678901
.NOTATION.....VAPOR DATA.....SHORT NAME... Y. A. J. xxxx.WEIGHT DATA.....FORMULA..#
.NOTATION FOR NONVOLATILES....SHORT NAME... Y. A. J. xxxx.WEIGHT DATA.....FORMULA..#
.NOTATION FOR UNNAMED COMPLEX STRUCTURES... Y. A. J. xxxx.WEIGHT DATA.....FORMULA..#
.NOTATION TO HERE ON 1ST CARD.SHORT NAME... Y. A. J. xxxx.WEIGHT DATA.....FORMULA..'
.NOTATION FOR VERY COMPLEX STRUCTURES CAN GO TO COLUMN 70 ON 2ND CARD.....FORMULA.."
.NOTATN REF.#8 REF.#7 REF.#6 REF.#5 REF.#4  R  CA RD REF.#3 REF.#2 REF.#1 FORMULA..*
```

The first 14 columns suffice to denote the structures of all appreciably volatile compounds, which must be relatively simple molecules, in terms of the systematic notation discussed in "Chemical Structure Notation." [With this line-formula notation, Smith *(12)* showed that *only ten or less* columns are necessary to describe 5580 of the 7105 most common chemicals—those listed in the Hodgman *(7)* and Lange *(9)* handbooks. Only *six* of these 7105 notations require more than 30 columns; and the longest notation (Lange No. 3732) requires only 41 columns *(12)*.] Next, 16 columns (15 through 30) are reserved for vapor data such as the critical thermochemical constants, or the vapor toxicity ratings described in "Toxicity Ratings"; hence the first 30 columns are reserved for the notation of nonvolatile compounds that also have a short name.

Short names, or the shortened systematic names described in "Short Name Identification" are carried in the next 13 columns (31 through 43) with occasional use of the preceding columns for prefix marks; thus, the first 43 columns can be wired directly to the corresponding alphabetic tabulator positions. Notations for unnamed very complex structures can, of course, continue to the 43rd punching column, as shown in the above symbolized examples.

For those rare "one in a thousand" compounds that have a very long structure description and a short name, a second chemical card is provided (and distinguished with its first part by a "zone" punch in column 80). The first 30 marks of the notation repeat on this card, and the notation continues as far as necessary, to the ultimate second card limit at column 70; the remaining nine columns (71 through 79) are reserved for a unique "serial number" identification which incorporates formula-indexing numbers (in "Formula Index Numbers"). These extra cards, both for the notation and for multiple references, are interpreted without any blank spaces after columns 43, 47, etc., since blank spaces within the notation have specific meaning.

The field-overlapping principle that is illustrated above also can apply individually in all cases that require a second card. For example, the longest notation among 7105 handbook compounds (Lange No. 3732) requires 41 columns and has a short name identification (Fast Red D); therefore the second card can carry the complete notation and all other data except the short name. Since all such second cards are identified uniquely with the first ones through the "serial number" in columns 70 through 79, no extra effort is necessary to keep these card pairs adjacent.

Column 80 carries two sets of punches: the numeric punches identify any one of nine different sets of cards, such as journal, reference, or chemical cards, and successive additions in the last set; the "zone" punches identify the first, second, or third card of its kind, for any multi-card entry within any set.

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While the punched cards are designed to be the primary information carriers, a great deal more can be done with them in an information center that has access to IBM accounting machinery. For example, a committee might want a few dozen Ditto copies of a list that summarizes all the references on just one chemical or one group of chemicals (selected, perhaps, by several independent sorting searches). In one rapid machine operation, the collected Reference Identification cards can be merged with the Journal Cards in such a way that each different "J-Code" among the Reference Identification cards is followed by that Journal Identification card. This merged collection of cards could "instruct" the tabulating machine to print the desired Ditto-masters at the rate of 9000 lines or cards per hour.

Similar lists can be made for any sequenced sets of cards. If the Reference Identification cards followed some sequence other than the "J-Code" letters, these letters could be wired to appear in any two letter-printing columns and the entire list of the explanatory Journal Identification cards could be issued separately. With standard IBM tabulators the only limitation is that the alphabetic (or letter-and-number) information must be printed in the first 43 columns of the list, since the remaining columns print numbers only. However, all three of these journal, reference, and chemical card layouts are designed with this limitation in mind, generally with the result that the pertinent alphabetic information never extends beyond a 43-column field.

After the listing operation, the cards can be sorted on column 80 for return to their respective catalogs. If the project were a continuing one, the selected cards first could be duplicated and kept in the listed order, ready to receive any occasional additions for future annual or monthly revisions.

This reference-listing example illustrates just one of the countless benefits (many of them unpredictable) that can be obtained from a punched-card cataloging investment.

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Table II. Preferences for Various Kinds of Toxicity-Coding Measures

(Figures in parentheses denote the percentage of toxicologists who replied to this question and favored the indicated measure)

	Definition of Toxicity Rating	*Total Favorability, %*
A.	Volatile hazards, measured as parts per million (p.p.m.) by volume	
	Concentration lethal to any animal in 5 to 10 minutes	21
	Narcotic concn. for rats (11), mice (7), other animals (4)	18
	Inhalation LD_{50} for rats (24), mice (14), dogs (4) after 4 hr.	42
	Tolerable, LD_0, for rats (7), mice (7), others (7) for 1 hour	21
	Threshold limit (M.A.C., max. allowable concn.) 8-hr. daily	57
B.	Threshold limit, in mg. per cubic meter of air	29
C.	Doses expressed as mg. per kg. of animal body weight	
	Single oral LD_{50}, rats (35), mice (25), dogs (11), cats (7)	75
	Single intraperitoneal LD_{50}, for rats (29), mice (29)	57
	Daily intraperitoneal LD_0, for rats (14), mice (29)	21
	Single dermal LD_{50}, for rabbits (32), mice (11), rats (7)	54
	Daily oral LD_0, tolerated by rats (39) or mice (14) for period of 1 mo. (4), 3 mo. (7), 6 mo. (7), 12 mo. (4), 18 mo. (4), 24 mo. (7)	50
D.	Feed tolerance, as weight parts per million of feed	
	Safe limit, LD_0 after 1 month, for rats (25) or mice (4)	32

Toxicity Ratings

Toxicity determinations require costly laboratory investments, so correlation of scattered information is desirable as much as possible, but the data have negligible correlating value unless the test conditions are standardized. Four essential test specifications are method of administration, test species, criterion of toxicity, and definition of measured units. Many possible variations must be reduced to a small number of standard combinations if the information is to be coded and correlated. Thus, the National Safety Council plan *(3)* employs five standardized toxicity tests to evaluate shipping hazards with a safe minimum of testing investment.

Table II summarizes the preferences for a dozen different toxicity ratings, as revealed by the responses to the questionnaire. Most of these are further qualified by preferences for the test animals, shown by the figures in parentheses. Even when test conditions are specified, imperfect experimental techniques may

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cause misleading results. For example, a strong minority of the toxicologists objected to intraperitoneal administrations, particularly for repeated doses, because adhesions or other complications might increase the mortality. The purity of the test chemicals also should be stated, since lethal quantities of impurities obviously would have their effect.

Toxicologists repeatedly have cautioned against deceptive "precision" in the *LD* values, which are misleading because of the inevitable variability of individuals receiving the doses—as well as those giving them! For example, Craver and associates at Ciba summarized many subtle causes of response variations when doses were administered intravenously to rodents *(4)*.

The numeric values used in this proposed toxicity registry (Tables III and IV) are based on a very simple grading system developed by Smyth and associates at the Mellon Institute *(14)*. Their "range-finding" numeric grades have three valuable attributes for punched card notation and correlation:

1. a tabulating mark (number or letter) suffices to show the value.
2. The geometric intervals defined by these marks permit simple comparisons among different sets of toxicity ratings (as on logarithmic scales).
3. The magnitude of the intervals—approximate powers of two—properly defines the limit of accuracy for the vast majority of published figures.

Most of the toxicologists who replied to the questionnaire acknowledged the need for a standard set of "pure number" intervals such as these, suitable for coding the magnitude of the dose in parts per million, in milligrams per cubic meter, or in milligrams per kilogram of body weight.

Single code marks for 30 successive grades of dosage are as follows:

Mark	*Mean Value*	*Mark*	*Mean Value*	*Mark*	*Mean Value & Exact Range*	
ø	500,000	&	500	#	0.5	0.36–0.69
1	250,000	A	250	J	0.25	0.18–0.35
2	125,000	B	125	K	0.125	0.09–0.17
3	63,000	C	63	L	0.063	0.045–0.089
4	32,000	D	32	M	0.032	0.022–0.044
5	16,000	E	16	N	0.016	0.011–0.021
6	8,000	F	8	⊖	0.008	0.0056–0.010
7	4,000	G	4	P	0.004	0.0028–0.0055
8	2,000	H	2	Q	0.002	0.0014–0.0027
9	1,000	I	1	R	0.001	0.0007–0.0013

On the IBM card, the three numerically parallel sets of values are distinguished by the top "zone" punch (denoted as &) and the second "zone" punch (denoted as #). Tabulated zero numerals can be distinguished from O-letters with care, but their identities are ensured by "slashing" the zeros and "barring" the O's. On the cards the punched positions alone are sufficiently distinctive.

Similar grades of dosage values, with a slightly smaller geometric interval of 1.5, were proposed by Deichmann and Mergard *(5)*, while larger intervals were proposed by Drinker and Cook *(6)*.

Table III. Structure Measures Favored for Toxicity Registry

(Parenthetical figures denote the percentage of those who replied to the question and favored the indicated measures)

(79)	Number of C atoms in compound	(74)	Presence of N atoms in compound
(51)	Number of H atoms in compound	(68)	Presence of S atoms in compound
(47)	Number of O atoms in compound	(21)	Presence of aromatic character
(37)	Number of RINGS in structure	(74)	Presence of HALOGEN atoms
(37)	Number of unsaturations	(32)	Presence of triple bonds
(16)	Number of "branched" atoms	(27)	Presence of quaternary atoms
(32)	Number of functional or alkaryl units in structure	(11)	Presence of METALLIC atoms
		(12)	Presence of heterocyclic rings

Table IV. Types of Structure Identification Favored for Toxicity Registry

(Parenthetical figures denote the percentage of those who replied to the question and favored the indicated measures)

(39)	One suitable for use with edge-notched (hand-sorting) cards.
(56)	One suitable for use with punched cards and tabulating machinery.
(26)	An agreed name of not more than ten (9), or of any number (4) of letters.
(13)	A natural "classifying" number of two (4) or any number (4) of digits.
(39)	A complete description, in linear (17) or two-dimensional (9) printing, based on a 40-character (13) or 80-character (4) keyboard, and on "line-formula" (22) or "root-naming" (4) principles.
(4)	A binary—present or absent—identification of "functional" groups.

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Table V illustrates the use of the single IBM marks to show toxicity ratings (in parts per million by volume) of some common vapors, along with the line-formula notation (see "Chemical Structure Notation") and the "shortnd" names (see "Short Name Identification").

The seven kinds of toxicity ratings shown in Table V can be carried in the columns of the "chemical identification" cards as indicated below:

Col. 15,	Concentration lethal to any animal in 5 to 10 minutes	(P.P.M. units)
Col. 17,	Concentration lethal to man in 30 to 60 minutes	(P.P.M. units)
Col. 19,	Concentration intolerable to man for 10 minutes	(P.P.M. units)
Col. 21,	Concentration tolerable to man for 1 hour	(P.P.M. units)
Col. 23,	Threshold limit (maximum allowable concentration)	(P.P.M. units)
Col. 25,	Irritant or nuisance threshold	(P.P.M. units)
Col. 27,	Odor threshold	(P.P.M. units)

Table V. Sample 43—Column Listing

```
COLUMN  1         2         3         4
12345678901234567890123456789012345678901234567890123

.NOTATION.....TOXIC RATINGS...SHORT NAME...

 0U101          5   7 B       ME  FORMATE

 0U1            5   & G       FORMALDEHYDE

 ZH           6 7   & B & C   AMMONIA

 NC1U1              E         ACRYLONITRILE

 SCS            8   & E   I   CBN DISULFIDE

 OSO            & E C F F G   SFR DIOXIDE

 GH             8   C G   D   HYD CHLORIDE

 FH           8 B   F G       HYD FLUORIDE

 R            5 6   7 D       BENZENE

 SHH          9 & C A E B J   HYD SULFIDE

 ONO          A B C   D C     NIT DIOXIDE

 NCH          A B D   F E I   HYD CYANIDE

 ZR                 B G       ANILINE

 WNR                A I   F   NITROBENZENE

 GG           A C D G I E G   CHLORINE

 G1V1         &   D     G     CHLORACETONE

 EE           9 C   G I J G   BROMINE

 I1V1         A           H   IODOACETONE

 GPGG         & C   G J I     P3  CHLORIDE

 E1VO2        A   F     I     ET  BR ACETAT

 GXGGOVG      C D C     J I   DIPHOSGENE

 E1R1         9   H     J   2 XYL BROMIDE

 WNXGGG       A B F     I I   CHLOROPICRIN

 1OSW01       B             I MS2 SULFATE
```

These successive measures follow a trend from high to low concentrations; this sequence provides more space in the notation field for complex compounds which

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could not exist in the high concentrations that are given in columns 15 and 17.

Narcotic concentrations apply only to relatively simple compounds that have very short line-formula notations; thus columns 12, 13, and 14 can be reserved to show narcotic concentrations for rats, mice, or man, respectively. Column 20 can show the inhalation LD_{50} for rats after four hours of exposure; and column 22, the tolerable LD_0 for rats after one hour. If revisions are necessary in any of these toxicity column assignments, the cards containing a mark in the questioned columns can be sorted out quickly and the revised layout can be reproduced automatically. This chemical card layout is the result of several such revisions.

The tabulating applications, such as the direct creation of Ditto masters at the rate of 9000 complete lines per hour, are of sufficient potential value to justify special consideration. (For example, the two separate components of the IBM letter punches can be sensed to print the two-column numeric equivalent of Smyth's toxicity grades.) In some standard tabulators, the "zone" punch for the 0.5 value (denoted here as the # mark) may print as a zero; while this #-zero could hardly be mistaken for the top 500,000 value, it might be confused with the O-letter (a very slightly narrower figure in the IBM type) since this mark represents the 0.008 value. To avoid any such tabulating ambiguities, the # mark should be replaced by the J punch in the few places where the 0.5 value is coded; then on the punched card itself, the lower component of this J-punch (position 1) can be circled to show that the true rating is 0.5 rather than 0.25, if such refinement is justified.

Toxicity ratings *in weight units* apply to the most complex structures in the registry. Therefore all weight ratings are given in the right-hand part of the card, outside the notation-vapor-name field illustrated in Table V. (Here again the letter punches could be sensed in two parts to print a two-column numeric grade.)

Weight ratings for radioactive substances extend beyond the 0.001 value —for example, in milligram units—so all tabulating ambiguities among single-mark symbols can be avoided by using S for the 0.0005 value, T for 0.00025, etc., to Z for the least possible 0.000004 value. Thus, the mark U or value 0.00012, in *milligrams per body units*, represents the maximum amount of radium (0.1 microgram) that could safely be deposited in the human body. The plutonium limit in these same units is represented by the R mark (1 microgram); and in contrast, the normal 50-gram salt content of the human body is represented by the numeral 3 (50,000 mg.).

These single-mark equivalents of Smyth's "range-finding" grades provide sufficient capacity on the chemical-information cards for 16 different toxicity ratings by weight, in addition to the three fields of information illustrated in Table V. Physicians' doses may be included among the weight ratings, since these values obviously are conservative measures of safe body tolerances. Columns 55 to 70 are reserved for these above mentioned 16 different ratings. The equally concise structure descriptions may extend from the first few columns (for common solvents) to the 43rd letter-printing column (for exceedingly complex drugs).

Chemical Structure Notation

The line-formula notation featured in this punched-card catalog also has been used independently by Benson *(1)* to code 3500 Eastman chemicals on Remington-Rand cards, and by Smith *(12)* to code over 7100 *Handbook* chemicals on IBM cards at the University of Hawaii. Smith employed the systematic contractions that are explained in the fully detailed manual for this notation *(15)*, and demonstrated that 80% of the *Handbook* structures *(7, 9)* could be described with ten or less punched-card columns. Smith and Benson also made statistical studies which showed, for example, how well the first *two* marks of this line-formula notation divide the 7100 *Handbook* chemicals among several hundred functionally distinct subclasses.

Table VI illustrates the specific letter symbols which, with the generic alkyl-group symbol, A, describe common aliphatic structure types. Specific alkyl groups are distinguished by arabic numerals which denote the number of carbon atoms in these chain units. Unsaturations are indicated by colon marks in typewritten or

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printed copy, or by the letter U in punched-card equipment. Thus, ethylene is 1:1, acetylene is 1::1, and butadiene is 1:2:1.

Only two new specific letter symbols are necessary to describe the open-chain hydrocarbons: Y for the *ternary* carbon atom, and X for the quaternary carbon atom. These letters graphically suggest the corresponding bond patterns.

Only two additional new letter symbols are necessary to describe the thousands of aliphatic oxygen derivatives of these hydrocarbons: Q for the hydroxyl or OH group, and V for the very common carbonyl *connective*, the bivalent CO group.

Three new letter symbols are introduced with the nitrogen derivatives: K for the quaternary and cationic nitrogen atom, M for the imino or mid-amino NH group, and Z for the terminal or primary amino NH2 group (as in hydraZine).

Table VI. Descriptive Symbols for Common Aliphatic Structure Types

[Letter *A* denotes any alkyl(ene) chain or connective]

A. Unbranched Structures

AMA	*sec*-Amines	NNNA	Azides
AN:NA	Azo compounds	OCNA	Isocyanates
AOA	Ethers	O:A	Aldehydes
AOOA	Peroxides	O:NA	Nitroso compounds
AOVOA	Carbonates	PHHA	Phosphines
ASA	Sulfides	QA	Alcohols
ASSA	Disulfides	QOA	Hydroperoxides
A:A	Alkenes	QVA	Carboxylic acids
A:A:A	Alkadienes	SCNA	Isothiocyanates
A::A	Alkynes	SHA	Mercaptans
AVA	Ketones	SHVA	Thiolic acids
AVOA	Esters	S:A	Thioaldehydes
AVOVA	Anhydrides (acid)	WNA	Nitroalkanes
CNA	Isocyanides	WNOA	Nitrates
FA	Fluoroalkanes	ZA	*primary* Amines
GA	Chloroalkanes	ZVA	Amides
M:A	Imines	ZVAVQ	Amic acids
NCA	Nitriles	ZVMMA	Semicarbazides
NCOA	Cyanates	ZVMVA	Ureides
NCSA	Thiocyanates	ZVOA	Urethanes

B. Branched Structures (Containing *Ternary and Quaternary* Atoms)

ANA.A	*tert*-Amines	S:YA.A	Thioketones
AOPHO.OA	Phosphites	S:YA.SH	Dithioic acids
AOPOA.OA	Orthophosphites	S:YGA	Thioacyl chlorides
AOSO.OA	Sulfites	S:YQA	Thionic acids
AOSWOA	Sulfates	S:YZMMA	Thiosemicarbazides
AOYA.OA	Acetals	S:YZMN:A	Thiosemicarbazones
AOYOA.OA	Orthoformates	WNYA.:NQ	Nitrolic acids
ASXA,A.SA	Mercaptols	WSA.A	Sulfones
ASYA.SA	Mercaptals	WSA.OA	Sulfonates
AXA,A.A	Neoalkanes	WSGA	Sulfonyl chlorides
AYA.A	Isoalkanes	WSQA	Sulfonic acids
M:YA.OA	Imido-esters	ZMYA.:M	Imidrazides
M:YGA	Imide chlorides	ZNA.A	*as*-Hydrazines
M:YZMA	Guanidines	ZN:YA.A	Keto-hydrazones
OAsA,A.A	Arsinoxides	ZN:YA.MZ	Hydrazide-hydrazones
OKA,A.A	Amine oxides	ZVNA.A	*as*-Ureas
QXA,A.A	*tert*-Alcohols	ZYA.:M	Amidines
QYA.A	*sec*-Alcohols	ZYA.:NQ	Amidoximes
QYA.OA	Hemiacetals	ZYA.:NZ	Amidrazones
QYA.:M	Imidic acids	ZYA.:S	Thionamides
QYA.:NQ	Hydroxamic acids	ZYVQ/A	L-*alpha*-Amino acids

Sulfonyl and nitro groups introduce the symbol W for the nonlinear "dioxo" or O_2 part of these functional groups. Finally, the two most common halogen atoms are denoted by distinctive single letters which facilitate machine operations (see "Binary Searching Field"): G for the chlorine atom, avoiding the typewriter ambiguity in Cl, and E for the bromine atom. Thus, hydrogen and the halogens fall within an alphabetically compact E, F, G, H, I sequence—to which J can be added for a "jeneric halojen"!

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The remarkably efficient discriminating power of these line-formula symbols is demonstrated by Smith's and Benson's statistical analyses: the *first two marks* divide the 7100 *Handbook* chemicals into 263 different "functional" groups, and 147 of these contain less than 0.1% of the catalog (less than 7 chemicals each). Benson's corresponding analysis of the 3500 Eastman chemicals shows surprisingly close agreement; thus, the percentages in the 24 *largest* groups compare as follows (Smith *vs.* Benson lists):

1O—	Methoxy compds.	1.2% *vs.* 1.5%	QR—	Phenols	4.3% *vs.* 3.8%
1R—	Tolyl compds.	1.2 1.2	QV—	Carbox. acids	8.2 5.8
1V—	Acetyl compds.	1.6 2.3	QY—	*sec*-Alcohols	1.8 1.2
1Y—	Isopropyl compds.	2.3 1.7	WN—	Nitro compds.	6.6 6.0
2O—	Ethoxy compds.	2.8 2.8	WS—	Sulfo compds.	1.3 1.4
G1—	Cl-methyl compds.	0.8 1.2	ZR—	Aniline derivs.	5.0 4.0
GR—	Chlorophenols	0.8 1.2	ZV—	Amides, ureas, etc.	2.2 1.4
GV—	Cl-formyl compds.	0.7 1.5	ZY—	"*sec*-Amines," etc.	1.5 1.2
NC—	Nitriles	1.3 1.8	L—	(Carbopolycyclics)	2.1 1.5
OU—	Aldehydes	1.9 2.7	L6—	(Cyclohexyl, etc.)	6.5 6.5
Q1—	HO-methyl compds.	1.4 1.2	T5—	(Heterocyclics)	5.8 5.2
Q2—	HO ethyl compds.	1.4 1.2	T6—	(Heterocyclics)	6.0 5.2

Each of the remaining 239 two-letter subdivisions of the 7100 *Handbook* chemicals contains less than 1% of the catalog (less than 70 chemicals each).

Cyclic compounds other than simple benzene or polyphenyl derivatives constitute a surprisingly small fraction of the commonly met chemicals—only 23% of the 7100 *Handbook* chemicals, and only 26% of the 3500 Eastman chemicals. Thus the open-chain and benzene-ring derivatives must be recognized as the dominating types *among the commonly met compounds.* The chapter headings in general or advanced textbooks of organic chemistry reflect this same proportion. Even in the National Research Council's catalog of 50,000 biologically tested compounds, tetracyclic and higher ring systems constitute only about 2% of the total—and 1.4% of these are sterol derivatives!

The benzene ring is cited far more often than all other rings combined, so this singular prominence (even in the Beilstein Handbook) justifies the use of a single letter R for this resonating ring. All other ring systems are described with the well-known Ring Numbers; in the cycloalkyl derivatives, these are logically associated with the alkyl chain symbols, and in polycyclic systems, the ring numbers are cited in pictorially direct order. These numeric descriptions of ring systems all are distinctively enclosed in parentheses.

Lower case letters locate all ring positions through their alphabetic order; these "locants" constitute a logically distinct and very concise set of symbols. They establish the relative positional relations in a way that never can be confused with existing systems of "enumeration."

In May 1950, at the National Research Council's First Symposium of the Chemical-Biological Coordination Center *(10)*, the author privately discussed a way of using this line-formula notation in standard punched-card equipment. Briefly, the key idea centers on the use of a *blank space* within the punched-card notation—to convey "lower case" meaning if it precedes a letter (ideal with the locants), and "superscript" meaning if it prefixes a number (ideal for multipliers of radicals, as well as the necessary but infrequent isotope numbers). The Notation manual should be consulted for more elaborate details relating to structure descriptions.

The Binary Searching Field

There are 1369 possible combinations of the first two line-formula symbols (26 letters, 10 numerals, and the blank space). A few hundred of these would not appear if the notation is used according to the rules—e.g., "forbidden" combinations like 1Q— and Y1— when compounds of all elements are considered. Thus, the first two marks alone of the line-formula notation distinguish roughly a thousand subclasses in very large chemical catalogs. When *combinations of functional groups* are sought, however, even this enormous discriminating power is not enough. What is needed with standard punched-card equipment is a compact *binary*—i.e., present or absent—searching field: one that provides a fixed punching

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place for each elementary symbol in the structure description. A "binary" field shows present or absent, punched or unpunched, distinctions, as with edge-notched cards.

A four-column IBM field is sufficient when the elementary variables are the symbols of this notation, because there are 48 binary positions in these four columns, and only 36 single-mark symbols—like 2 for ethyl groups, 4 for butyl or cyclobutyl groups, Q for alcohols, V for ketones, and Z for primary amino or NH_2 groups. Thus, 12 additional positions remain for independent variables such as ionic nature, aromatic character, heterocyclic group, etc., and for a few very prominent two-letter groups such as carboxylic acids (QV) and esters (OV). The latter two assignments prevent overloading of the alcohol (Q), ether (O), and ketone (V) punches.

Table VII summarizes the assigned meanings for the 48 positions in this binary searching field. The numerals and capital letters are re-registered directly from the corresponding atomic group symbols in the IBM notation—e.g., both M and G for a Mg atom—except that the benzene "R" is punched in the upper (R) position. All positional designations are disregarded. The other parenthetically bracketed punching positions identified in Table VII are the additional semi-independent variables.

The discriminating capacity of this four-column binary field is enormous: if only 40 of the 48 structural distinctions were fully independent variables, these four columns could show 2^{40} or 1,000,000,000,000 combinations!

Columns 50 to 53 on the chemical identification cards are reserved for this binary searching field, as shown in Table VII. An additional column 54 is reserved to show multiple occurrences of any one symbol-punch in the corresponding horizontal row of the searching field. Thus the cards for polymethyl or polyphenyl compounds would have the 1-position punched again in column 54; polybromo or polyketo compounds, the 5-position; and polyhydroxy compounds, the 8-position punched again in column 54. (The vertical positions for the letter-punches are obtained directly from the lower components of the standard IBM letter-punches, and the three horizontal positions—columns 51, 52, or 53—are determined from the upper or "zone" components. Thus, all of the 36 notational symbols can be "regenerated" from the binary searching field for proofreading work, in a 36-column specially wired tabulation.)

Table VII. Binary Searching Punches

Col: 50	51	52	53	*Additional Punches (Bracketed Symbols)*	
(t)	(a)	(s)	(x)	(t)	Twenty or more C-atoms in alkyl group
(d)	(e)	(o)	(h)	(d)	Decyl to nonadecyl alkyl chains
ø	(i)	(q)	(c)	(a)	General *alkyl* group
1	A	J	(R)	(e)	Element or alloy
2	B	K	S	(i)	Inorganic compound
3	C	L	T	(s)	Salt or ion-pair compound
4	D	M	U	(o)	OV-ester (not punched in O or V)
5	E	N	V	(q)	QV-acid (not punched in Q or V)
6	F	O	W	(x)	Aromatic character in any ring besides R
7	G	P	X	(h)	Heterocyclic ring
8	H	Q	Y	(c)	Carbocyclic ring other than benzene-R
9	I	R	Z	(R)	Benzene ring

The lower R-punch (Col. 52-9) is reserved for R in the atomic symbol, as in CR.

Formula Index Numbers

The results of the author's questionnaire shown in Tables III and IV demonstrate that the structural measures are still favored as searching tools for chemical catalogs and include those used in the *Chemical Abstracts'* Formula Indexes and Ring Indexes. Punched cards are ideal carriers for formula index numbers, because each atom count can serve as an independent searching and sorting aid, or classifying and filing measure. Subdivisions based on these atomic totals represent truly elementary distinctions that set broad, natural limits to the possible combinations of functional groups. For example, a search for halogenated nitro compounds must be confined to those sections of the Formula Index that contain at least one

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halogen atom, one nitrogen atom, and two oxygen atoms; the minimum total of at least four heteratoms also is a search-limiting measure.

Most structural searches can be focused to an astonishing degree by storing the cards on the shelf according to just two or three natural formula-indexing measures of small magnitude (less than ten) that are easily learned, quickly counted, and always remembered. A practical consequence of no small importance is that this elementary storage accelerates searches and retards card wear, because sections of the catalog that cannot contain the minimum elements obviously need not be passed through the searching machines.

Optimum sorting efficiency with IBM equipment is obtained when the actual formula numbers are reduced to a simpler set of numerical measures, each with probable values ranging from zero to nine. One such measure might be the number of oxygen atoms, up to nine and more in the final division. This measure gives a rather poor distribution among the high values, however; compounds with one to four oxygen atoms in the structure are far more probable than those with five or more oxygen atoms. If several equally simple atom-counting measures were found to give reasonably balanced population distribution among the ten-digit values of each measure, their ease of usage would clearly outweigh the slight loss in capacity due to imperfect distributions.

Four such formula file numbers have been found and tested in large indexes. The first number, designated as an A-digit, divides the *Chemical Abstracts* Formula Index into ten equally large or equally important *elementary* sections:

A-Digit	*Elementary Definition*	*Per Cent of Catalog*
0	Oxy-hydrocarbons (C,H,O only)	15.2
1	N_1 (C,H,O) compounds	9.2
2	N_2 (C,H,O) compounds	8.6
3	N_{3-N} (C,H,O) compounds	9.8
4	S (C,H,O) compounds	7.8
5	S,N (C,H,O) compounds	17.3
6	Halogen (C,H,O) compounds	7.9
7	Halogen,N (C,H,O) compounds	11.6
8	*All* other organic compounds	8.7
9	All inorganic compounds	3.9
	Total	100.0

The percentage figures indicate the distribution for the ten-year period from 1942 to 1951. The recent increases among P, Si, or F compounds might seem large within the 8.7% total of the A_8 division, but these little expansions have not disturbed the long-enduring dominance of the C, H, O, N, S compounds. Formula indexes from smaller general collections show a much smaller percentage in the A_5 division, and a much larger percentage in the first or A_0 division. Thus, the smaller catalogs reflect the dominance of the simpler combinations of elements.

A logical subdividing measure for these major elementary A-digit divisions is the *total heteratomic count*, designated as the T-digit and meaning all atoms other than carbon or hydrogen. It gives a somewhat better distribution than the O-atom count (with the same maximum of nine and more), and provides better correlations. Thus the T_1 division associates all simple alcohols, ethers, amines, and halides.

A third natural decimal measure that gives striking distributional uniformity is designated as the C-digit because it represents simply the units part of the long-featured carbon-atom count; that is, the digit 2 for C_2, C_{12}, C_{22}, etc., or C_{102}.

The data in Table VIII show how well some 994 randomly selected examples (the first compound on every even-numbered page of the *Chemical Abstracts*' Formula Indexes) are distributed among the 90 organic subdivisions defined by the A-digit and C-digit values. The effectiveness of these two simple decimal measures is proved by the large number of average-sized subdivisions. Only four of the ninety subdivisions contain more than twice the average (more than 20 compounds), and only five contain less than half the average (less than 5). Confirming proof of a profound statistical balance is evident in the last column of Table VIII, where the percentage figures show how well the C-digit itself divides the collection into ten almost exactly equal sections.

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Table VIII. Distribution of Compounds among A-C Subdivisions

(994 random organic examples from 1942–51 *C.A.* pages)

C-Digit Values	*A-Digit Values (Major Divisions)*										*C-Value,*
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*Subtotals*	*%*
0	20	9	11	12	14	17	11	8	9	111	11
1	16	8	12	8	*2*	19	*1*	18	7	91	9
2	12	6	8	18	10	18	13	14	10	109	11
3	20	8	10	9	8	10	6	13	3	87	9
4	14	12	9	7	14	18	11	8	11	104	10
5	13	8	11	11	*4*	9	9	13	6	84	8
6	10	12	9	7	5	**23**	11	13	**21**	111	11
7	19	6	7	12	9	16	6	14	*4*	93	9
8	17	14	5	9	6	**24**	8	9	16	108	11
9	15	13	8	8	9	**22**	6	12	*3*	96	10
A-Subtotals	156	96	90	101	81	176	82	122	90	994	99

A fourth numerical measure that is somewhat more difficult to understand is designated as the H-digit because it is integrated from the tens and units digits of the H-atom count. The units digit alone gives poor discriminating efficiency because *odd* numbers of H-atoms cannot occur among the compounds in the A_0, A_2, and A_4 elementary divisions; and *even* numbers cannot occur in the A_1 division. Therefore, the H-digit is derived from the true H-atom count as shown here:

H-Digit	*True H-Atom Count*										
0	0	...	19	28	37	46	55	64	73	82	91	100
1	1	10	...	29	38	47	56	65	74	83	92	101
2	2	11	20	...	39	48	57	66	75	84	93	102
3	3	12	21	30	...	49	58	67	76	85	94	103
4	4	13	22	31	40	...	59	68	77	86	95	104
5	5	14	23	32	41	50	...	69	78	87	96	105
6	6	15	24	33	42	51	60	...	79	88	97	106
7	7	16	25	34	43	52	61	70	...	89	98	107
8	8	17	26	35	44	53	62	71	80	...	99	108
9	9	18	27	36	45	54	63	72	81	90	...	109

The effectiveness of the four A, T, C, and H digits in independently decimating a comprehensive Formula Index has been demonstrated with the 6500 organic compounds in the Lange Handbook *(9)*, and with the 5500 in the Hodgman Handbook *(7)*. The 25 largest groups of compounds with the same empirical formula in either of these handbooks contain 10 to 29 members. These groups increased by an average of *only two* additional compounds when classified by the much simpler A-T-C-H digits. Furthermore, no new A-T-C-H divisions appear from other sets of formula isomers that are larger than these. This striking leveling effect of the four natural numerical measures is illustrated in Table IX.

Inorganic compounds contain no carbon atoms, so for these compounds, the C-digit indicates the largest periodic group number of the metallic elements in the given formula, up to the value 7 for the Mn group, 8 for the Fe group, and 9 for the Co group. Similarly, for these compounds, a redefined H-digit indicates the largest "contravalent" periodic group number, starting with 0 for the inert gases, 1 for the halogens, etc., and concluding with 8 for the Ni group. Thus the A-T-C-H number for $FeCl_2$ is 9-3-8-1, and that for $K_2Cr_2O_7$ is 9-9-6-2 (or just 9381 and 9962).

Ring Indexes also are important because rings characterize the structure and contribute peculiar chemical attributes like aromatic character. Fortunately, a single ring-indexing digit has been found that seems sufficient in itself to complement the four formula digits. This fifth measure is designated as the Ring-digit of B-digit (full sequence of digits gives a B-A-T-C-H number, a useful memory aid) because its divisions show an exact parallel with those defined by the A-digit—a parallel between numbers of benzene rings and numbers of nitrogen atoms, between other monocyclic compounds and sulfur compounds, between bicyclic compounds and halogen compounds, between tricyclic structures and all other organic formulas, and finally between the remaining polycyclic structures and inorganic formulas. This parallel is best understood by comparing the respective A- and B- definitions.

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Table IX. Analysis of Largest Formula Index Divisions

(All A-T-C-H divisions with more than 20 isomers in either the Hodgman or Lange Handbook lists)

No. in A-T-C-H Division		*A-T-C-H File*	*Largest Formula*	*No. in Largest Formula Division*	
Hodgman	*Lange*	*Numbers*	*Division*	*Hodgman*	*Lange*
27	31	0291	$C_9H_{10}O_2$	25	29
24	28	1182	$C_8H_{11}N$	23	26
22	28	0203	$C_{10}H_{12}O_2$	20	26
27	27	0388	$C_8H_8O_3$	27	27
18	26	0287	$C_8H_{16}O_2$	15	22
26	7	0075	C_7H_{14}	24	5
25	23	0005	$C_{10}H_{14}$	21	20
20	24	0165	$C_6H_{14}O$	20	23
19	23	6264	$C_6H_4X_2$	18	22
23	13	0063	C_6H_{12}	19	9
22	22	0263	$C_6H_{12}O_2$	21	21
22	21	0281	$C_8H_{10}O_2$	21	20
10	22	6189	C_8H_9X	10	22
19	21	0177	$C_7H_{16}O$	18	19
19	21	0251	$C_5H_{10}O_2$	13	15
5	21	6446	$C_{14}H_6O_2Cl_2$	3	13

Sizes of these formula divisions increase in proportion to the *square root* of the list size; thus the largest formula divisions in the 500,000-item *C.A.* Cumulative Formula Index contain around 200 isomers each.

The impressive labor-saving power of the decimating numeric measures can be illustrated with a single example—a deck of 10,000 cards can be reduced to 1000 by sorting on the first specified digit; these 1000 cards in turn can be reduced to 100 by the second digit, and the 100 to 10 by the third digit. The total number of card-passes through the sorter is only 11,100—a mere twenty minutes of machine time with a standard model that processes 650 cards per minute!

If cards were made for each of the 500,000 chemicals in the *Chemical Abstracts* Cumulative Formula Index, and if these were stored by rows and columns in accordance with the C-digit and A-digit values, the largest resulting A-C partition would contain some 12,000 cards (see Table VIII). Thus in a formula-index search, this largest segment would be reduced to a mere dozen or so by three simple sorting operations on the remaining B-T-H decimating numbers.

Comprehensive searching and correlating versatility could be made available in a *ring-formula* catalog, stored by the B- (ring) and A-digits, for the resulting B-A partitions follow an idealized Beilstein arrangement. In this ring-digit array of cards, an eleventh "top" B-row would appear for all chemicals with an undefined or *blank* value in the B-digit position. (In this same row, the blank A-digit position provides a specific place for drugs of undetermined empirical formula.)

Columns 71 to 75 in the "chemical identification" cards carry these B-A-T-C-H numbers that provide a "streamlined" ring-formula index; columns 76 to 78 in this field are reserved for supplementary serial designations—arbitrary number or letter assignments—that provide concise yet fully specific identifications for all catalog entries, regardless of name or notation. (If letters and numbers are used in columns 76 to 78 for the above-mentioned drugs of undetermined empirical formula, more than 39,000 designations are provided, without any O or I ambiguities.)

These ten equally important cyclic divisions therefore are as follows:

Ring-Digit (B)	*Definition*	*% of Catalog*
0	Open-chain structures	21.5 (14)
1	Monophenyl derivatives	20.8 (23)
2	Biphenyl or bis-phenyl derivatives	8.1 (11)
3	Polyphenyl and benzoquinone derivatives	1.3 (4)
4	Other monocyclic structures	11.1 (8)
5	Monocyclic-(poly)phenyl derivatives	9.4 (10)
6	Bi- or bis-cyclic structures (nonphenyl)	10.7 (12)
7	Bi- or bis-cyclic structures with (poly)phenyl branches	5.4 (8)
8	Tri- or tris-cyclic structures, with or without phenyl-ring branches	7.7 (7)
9	All other multi- or poly-cyclic structures (and phenyl branches)	3.9 (3)

The B_6 and B_7 divisions include bis-monocyclic structures like nicotine, as well as the bicyclic structures like naphthalene. Likewise, "tris-cyclic" structures

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include tris-monocyclic and bicyclic-monocyclic combinations as well as the rarer tricyclic systems. Bis-bicyclic combinations thus belong in the last and smallest division. If the ring divisions were not defined in this "integrated" manner, the large ones would become still larger, and the small ones still smaller.

The first column of percentage figures represents the distribution found for the 50,000 biologically tested compounds that are cataloged in the National Research Council's Chemical-Biological Coordination Center *(10)*. The figures in parentheses represent the corresponding distribution in the larger but less representative Beilstein Handbook (many of these are merely identification derivatives).

Only 0.6% of the NRC-CBCC compounds are tetracyclic and larger systems other than sterol derivatives; some 1.4% are steroids, and the remaining 1.9% in the B_9 division consists of bis-bicyclic, etc., combinations.

Short Name Identifications

The last 13 columns of the 43-column Notation field on the "chemical identification" cards are reserved for a short name identification when one is established. Thus, if a very complex structure has no short name and requires 30 to 43 columns for its notation, no card capacity is lost; and in the few cases where such a very complex structure has a short name like hemoglobin, the complete structure description is given on a second card (see discussion in "Toxicity Literature").

Short name identifications, though seldom systematic, have remarkable survival strength; and this endurance is a proof of their continuing usefulness. For example, more than a century ago, many index entries for organic treatises were names like acetal, acetone, acetic acid, aconitic acid, acroleine, adipic acid, alcohol, alizarine, allantoine, and alloxan. These convenient word identifications still are the main entries for these compounds in the latest *Merck Index* (with no spelling change other than possible loss of the terminal *e*).

Inorganic crystallographic types likewise still are identified by chemically unrevealing names such as the diamond, zinc blende, zincite, fluorite, diaspore, cuprite, pyrite, ilmenite, calcite, and perewskite forms. These old-fashioned mineralogical names are useful particularly in cases where the formula alone is insufficient to identify polymorphous solids.

Forensic medicine undoubtedly continues to perpetuate legally established word identifications such as atropine, cocaine, curarine, hemoglobin, heroin, morphine, reserpine, and strychnine. "Systematic" names for these structures certainly can be devised, but they would be so complex and forbidding in appearance that their usefulness would be extremely difficult to demonstrate. In contrast, these established names are virtually indispensable dictionary identifications.

Pesticide name identifications like the recently assigned aldrin, allethrin, chlordan, dieldrin, heptachlor, lindane, malathion, methoxychlor, parathion, schradan, toxaphene, and warfarin have a far-reaching practical value that hardly needs elaboration.

All of the above names are sufficiently concise to be printed in the provided 13-column name field. Thousands of longer names also can be contracted to this size through the omission of terminating letters, or through the use of very simple combinations such as *the international atomic symbol plus its valence number*, when this identifies the *first* part of a name.

Many names for salts and esters consist of just two parts; punched-card operations on *both* parts obviously can be made if the first part is confined to the first three columns, and the second part to the last nine columns of a 13-column name field. A numeral in the third column can represent either the valence of a symbolized metallic ion, or the multiplicity of a monovalent radical. Thus the contraction

AG	CHLORIDE	means silver chloride
BU2	OXALATE	means dibutyl oxalate
ET	LINOLEATE	means ethyl linoleate
FE2	SULFATE	means ferrous sulfate
FE3	CHLORIDE	means ferric chloride
ME3	PHOSPHATE	means trimethyl phosphate

Table X contains some of the hundreds of anionic or terminating names—like -ANILINE, -BENZENE, -PYRIDINE, or -THIOPHENE—that can be suitably identified within the last nine columns (35 to 43) of the name field. The *iso* prefix

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is contracted to the letter *I* in both parts of the name, as in IBU ICYANATE and IPR IVALERATE. Likewise, the chloroacetate names are contracted to CL1ACETAT, CL2ACETAT, and CL3ACETAT. The name for the AsS_4 anion similarly is contracted to S4ARSENAT, and analogous compound names are contracted in the same manner.

Table X. Short Anionic or Terminating Names

Acetate	Cinnamate	Hyponitit	Oleate	Soyate
Aconitate	Citrate	Hypopsfat	Osmate	Stannate
Acrylate	Cyanamide	Hypopsfit	Oxalate	Stannide
Adipate	Cyanate	Hyposlfit	Oxanilate	Stannite
Alum	Cyanide	Ibutyrate	Oxide	Stearate
Aluminate	Decoate	Icyanate	Palmitate	Stibnate
Amide	Dichromat	Icyanide	Perborate	Stibnite
Anisate	Dioxide	Iodate	Perbromat	Succinate
Anthranlt	Disulfide	Iodide	Perclorat	Sulfanlat
Arsenate	Ethoxide	Itaconate	Periodate	Sulfate
Arsenide	Ferrate	Ithiocynt	Permangnt	Sulfide
Arsenite	Ferrite	Ivalerate	Peroxide	Sulfite
Azide	Fluoborat	Lactate	Perphsfat	Tannate
Benzoate	Fluocrmat	Laurate	Persulfat	Tantalate
Bicarbnat	Fluosilat	Levulinat	Perthiont	Tartrate
Bifluorid	Fluotitat	Linoleate	Phosphate	Telluride
Bismate	Fluoride	Linoresnt	Phosphide	Tellurite
Bisulfate	Formate	Maleate	Phosphite	Thiocyant
Bisulfide	Fulminate	Malonate	Phthalate	S4Arsenat
Bisulfite	Fumarate	Mandelate	Picramate	S4Bismate
Borate	Furoate	Manganate	Picrate	S3Stannat
Boride	Gallate	Manganite	Platinate	S4Stibnat
Bromate	Germanate	Mercaptan	Platinite	Thoriate
Bromide	Gluconate	Methacrlt	Plumbate	Titanate
Butyrate	Glutamate	Molybdate	Plumbide	Toluate
Carbamate	Glutarate	Myristate	Propionat	Tungstate
Carbide	Glycphsft	Naphthent	Resinate	Uranate
Carbonate	H4Borate	Naphthoat	Rhenate	Valerate
Caseinate	Hafniate	Nicotinat	Ricinate	Vanadate
Cerate	Heptoate	Nitrate	Salicylat	Xanthate
Chlorate	Hexoate	Nitride	Sebacate	Zincate
Chloride	Hippurate	Nitrite	Selenate	Zirconate
Chlorite	Hydride	Nonoate	Selenide	
Chromate	Hydroxide	O acetate	Selenite	
Chromite	Hypoclrit	Octoate	Silicate	

Numeral is a multiplier of preceding symbol: H4Borate is tetrahydroborate.

Initiating symbols ME, ET, PR, BU, AM or PE, HX, HP, and OC should be obvious contractions for the *n*-alkyl names. Like AC, BZ, and PH, these two-letter symbols can be combined with a numeric multiplier in column 34; but the multiplier must be omitted for three-letter contractions like ALY (allyl), AMI (amino), AMM (ammonium), BZL (benzyl), DEC (decyl), ICY (isocyano), IPR (isopropyl), LRL (lauryl), NON (nonyl), TOL (tolyl), and the like.

Prefixed letters or numbers precede the name field; thus in column 29 the lone letter M is *meta*, O is *ortho*, P is *para*, R is *racemic* or *dl*, S is *secondary* (or *symmetric*), T is *tertiary*, and V is *vicinal*. A contracted name like 2356BR4 Phenol would begin in column 27, thus should be understood to mean 2,3,5,6-tetrabromophenol.

Dyes, indicators, and pigments usually earn names that have an obvious practical meaning, such as Aniline Black, Bismark Brown, Indigo Blue, Guinea Green, Butter Yellow, Methyl Orange, Lithol Red, Methyl Violet, and the recently popular Methyl Purple. Where the name ends in the color identification, as in these cases, the color correlations can be made with punched cards by using the *last* three columns (41 to 43) for code words such as RED, ORG, YEL, GRN, BLU, VLT, PRP, BRN, BLK, and WHT. These are used only as parts of the name, not as physical descriptions.

The name contractions suggested in this section do not add any system to the seemingly chaotic collection of established word identifications—nor is any systemization intended. Instead, the naming procedures should be kept as liberal and flexible as possible, so that eventual improvements are not excluded. At the present state of development, the short name should supplement or complement

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the systematic notation and the formula numbers in the same way that a "bird's-eye view" supplements an architectural floor plan and the side views.

If a research preparation has no common name and no commercial value, but can be described precisely by the systematic notation, classified by this notation and the prefix mark, cross-indexed by the formula-ring numbers, etc., then the "need" for a name that is nothing more than a spoken constitutional formula seems to be more imaginary than real in this catalog. If the notation is short, and the corresponding systematic name can be contracted to fit within the 13-column name field (not counting prefix numbers), this is a welcome confirmation, but not a necessity.

Acknowledgment

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Trends in Pharmaceutical Advertising

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The character of pharmaceutical advertising has undergone marked changes with the emphasis now being placed on service to the medical profession. Industry is also exhibiting awareness to public opinion with many companies adopting or expanding public relations. These trends are illustrated primarily in terms of advertising.

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In an age in which the commercial singing or otherwise has become a symbol of advertising, the character of ethical pharmaceutical advertising seems indeed paradoxical. The word "commercial" applies strictly to consumer advertising and connotes a message from the advertiser to note the advantages of a product.

This is a relatively simple approach to the problem of selling and apparently an effective one in the consumer field. It is, however, an approach that is taboo in ethical pharmaceutical advertising for several good reasons.

For one thing, television, radio, and other consumer media suitable for this kind of promotion are usually out of bounds to the advertiser of ethical pharmaceuticals. Obviously, the latter must limit his advertising to professional people—the doctors who will prescribe his product, the medical students who are potential prescribers of his product, or the druggist who will dispense his product. In most instances, these groups resent being approached through anything but ethical media. Furthermore, the exaggerated, repetitious claims of the advertising "commercial" are not favorably received by a well-informed and discriminating professional audience. Ethical pharmaceuticals must be promoted in the language of science. A precise and often complex language is distinguished by reservation rather than exaggeration and cannot be effectively translated into consumer advertising jargon.

There is another important difference between the consumer advertiser and the advertiser of pharmaceuticals. The consumer advertiser is almost exclusively concerned with promoting either his products or premiums which help to sell his products. The pharmaceutical advertiser, although equally concerned with selling his product, has found it advantageous to operate beyond the level of pure product promotion. On a second level he performs a vital function—that of providing service.

Services by Pharmaceutical Advertiser

Services performed by the pharmaceutical advertiser consist mainly in keeping the doctor informed of current medical developments, telling him how to use pharmaceutical products and, in general, helping him to practice medicine. The prescribing of modern pharmaceuticals and the practice of modern medicine require a broad background of information and entail extremely complicated techniques. If the advertiser's product is to be integrated into the pattern of modern medical practice, and if the good will of the prescribing customers is to be obtained, the pharmaceutical advertiser must perform services for the doctor. In so doing, he serves his own cause.

Of course, all services offered by the pharmaceutical advertiser do not meet the criteria. In a highly competitive business, good will is vastly important. And almost any means of obtaining it—within the limits of ethical practice—is considered cricket. Under certain circumstances, good will may be had by catering to the doctor's cultural interests, or other interests outside the field of medicine.

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Scientific Publications

Of the services performed by the pharmaceutical advertiser, perhaps the most outstanding is in the field of scientific publications. Almost every major pharmaceutical house publishes a magazine or "external house organ" which is mailed regularly to doctors, medical students, and others—usually without charge. These magazines cover a wide range of subject matter of general or special interest to practicing, researching, or teaching physicians, and are distinguished in several instances by elaborate and unusual application of art.

A recent issue of the *Lederle Bulletin*, published by Lederle Laboratories, demonstrates the character of this type of service. An article entitled "Medico-Economic Frontiers: Population Movements" presents a detailed account of mass migrations which have occurred in this century and outlines medical measures undertaken to safeguard the health of the migrants. This same issue carries, among other things, a lengthy article on recent advances in ophthalmology and a series of detailed, fully colored illustrations of the female reproductive organs. Product promotion is not evident in either of these features, although several other articles refer, directly or indirectly, to Lederle products and advertisements of the company's products appearing in the issue.

In another publication, *Scope*, published by the Upjohn Co., an article entitled "Telling Lines—Some Notes on Graphs" appears in a recent issue. This article deals with the history and development of various types of graphs and their role in modern scientific procedures.

As with the *Lederle Bulletin* this issue of *Scope* carries advertising, but the emphasis is on material offered primarily as a service.

Abbott Laboratories' *What's New* is perhaps the best known service of this company to the medical profession. The emphasis is definitely on art, even to an accompanying text by a well-known art critic. Subject matter of *What's New* sometimes ranges far afield of medicine, an indication that Abbott relies heavily on cultural appeal as a means of cultivating good will. One issue of *What's New*, for instance, carried short stories by Emily Kimbrough and J. Frank Dobie, poems by Christopher Fry and the late Jan Struther, an original painting by Rouault, and the score for an original song composed by Harold Rome!

Newest of the pharmaceutical industry's house organs, and in some ways the most unusual, is *Spectrum* published by Pfizer. This publication is issued biweekly and is incorporated into the advertising pages of the *Journal of the American Medical Association*. Picking an issue at random, the following subjects were found to be discussed:

Current Emphasis on Eclampsia
Swimmer's Itch
How about the Southwest for Asthma

Motion picture films, such as those offered by Davis and Geck, Squibb, and Wyeth, have become established in the pharmaceutical industry's promotional program. These films are teaching aids covering diagnostic procedures, surgical techniques, and methods of treatment. The education of the patient is a service not neglected by the pharmaceutical industry. Brochures, pamphlets, and other printed material are made available through the medical profession. Examples of these include a handbook for diabetics offered by Squibb and dietary instruction sheets prepared by Meade Johnson.

Somewhat more elaborate general presentations, summarizing certain phases of the practice of medicine, have been distributed to physicians. These are offered gratis or at cost. Examples include the well-known *DeReMedica* of Lilly and *The Merck Manual*.

At Ciba the accent on service is perhaps even more pronounced than elsewhere in the pharmaceutical industry. Looming large among Ciba services is the *Clinical Symposia*, a magazine distributed six times a year, without charge, to a comprehensive list of doctors, medical students, and others interested in medicine. *Clinical Symposia* was inaugurated in the spring of 1948 with its objective, in the words of its editor, J. Harold Walton: "to present comprehensive, authoritative articles on subjects of general medical interest, in a simple and concise style—free from the esoteric terminology of the specialist." In mid-1949, a policy was inaugurated

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under which *Clinical Symposia* would accept only articles signed by recognized medical authorities. This policy has been followed strictly. A curious and striking fact is that, even though no fees are paid for articles, a wealth of material is almost always submitted for publication.

Selection of Articles

Subject matter for the *Clinical Symposia* is chosen with two broad considerations in mind; first, does the subject lend itself to illustration; second, is the subject of wide interest to the medical profession? The second consideration springs from the nature of the reading audience which is made up of 90% or more of general practitioners or specialists in fields other than that concerned in any particular article. The first consideration is guided by the trade-mark of *Clinical Symposia*—the illustrations of Frank Netter, who has gained recognition as one of the world's foremost medical illustrators. His range of talents has been expressed in a variety of subjects, such as hemorrhagic problems in infants and children, diseases of the uterus, pathology of the mouth and jaws, disorders of the hip, and others. He combines the artistry and craftsmanship of the illustrator with the scientific insight of the trained physician.

Two bound volumes of Netter's work, "The Ciba Collection of Medical Illustrations" and "Nervous System," contain drawings reproduced in elaborate color plates. The accompanying text is written by experts in various fields of medicine on commission from Ciba. Both of these books are distributed free to medical school libraries, and can be purchased by individual doctors or students at cost. These illustrations of Netter have also been reproduced on 35-mm. Kodachrome slides. Sets of these slides, containing all of the work of these two books, are sent without charge to all medical schools, and are also available—singly or in sets—to individual doctors at cost.

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Illustrative Material

These illustrations of Netter have also been reproduced on 35-mm. Kodachrome slides. Sets of these slides, containing all of the work of these two books, are sent without charge to all medical schools, and are also available—singly or in sets—to individual doctors at cost.

Ciba, as others in the pharmaceutical industry, considers product literature an indispensable service. For every product in the Ciba line, a detailed booklet or pamphlet provides all pertinent information on clinical experience with the drug, chemical and pharmacologic properties, experimental evidence, indications and contraindications, dosage, and precautions. A review of the general field of therapy is often included. When a new product is introduced, literature is particularly important. In this case the pharmaceutical advertiser is certainly the best source of information on the product and his responsibility is to convince the doctor of the value of the product. All possible dangers from using this product, necessary precautionary measures, and other factors which may circumscribe its clinical application, must also be pointed out. The ethical standards of any pharmaceutical house are certainly put to the test in its product literature.

Product literature is obviously a service that helps the doctor practice medicine—assuming that the product in question *is* good medicine. At Ciba, the Advertising Division makes available such things as a slide rule for determining hormone dosage, a slide rule for converting apothecary to metric system (and vice versa), record forms for patients undergoing sulfonamide therapy, and a series of maps showing geographical and seasonal patterns of allergy. The advertising staff also helps to prepare scientific exhibits which are shown at various conventions.

Exhibits

In these technical exhibits, Ciba has gone beyond a strict concept of product promotion and into the realm of service—for example, an exhibit on hypertension shown at the last A.M.A. meeting and scheduled for showings at future conventions. This exhibit was created by George Krajian, an Australian designer who is rapidly becoming famous for his original and highly complex work in Acrilac (a substance similar to Plexiglas). A series of superimposed acrilac sheets—intricately carved, stained, and synchronized with light and sound—has been prepared to demonstrate

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the basic phenomena of normal blood pressure and hypertension and the application of Ciba's three hypotensive drugs—Apresoline, Regitine, and Esomid. The result was a graphic, 15-minute course on the nature of hypertension and the effect of the newer drugs in this condition.

Another very important part of this company's program of service is *Cibascope*—a publication directed to all retail and hospital pharmacists and to all wholesale and chain drug stores four times a year. Besides information on various Ciba specialties, it features articles having to do with manufacturing or research activities of the pharmaceutical industry, the history of pharmacy, and other aspects of the profession. One issue carried a picture story describing medical and pharmacy facilities aboard the *S.S. United States.* In another issue, a story dealt with medical installations on United States Navy submarines. Favorable response to *Cibascope* has come from as far as Okinawa and Honolulu.

Another Ciba service appealing to interests other than medicine is the "Guide to New York City"—a 60-page book prepared originally for the A.M.A. convention. This book has now been reprinted and is available for future medical meetings in New York. Among other things, points of interest in New York, shopping, transportation and hotel facilities, and restaurants are covered.

A newcomer to the list of Ciba service is *Ciba Reports*—a newsletter devoted to highlights of important scientific meetings. At all of these meetings, correspondents cover the news, bringing physicians up to the minute on developments which might not be reported in other media. Reports from current medical literature are also included in this publication when appropriate. Sample headlines give an idea of the variety of its coverage:

One in Forty Pediatric Patients May Be Epileptic
Alcoholics Like Guns
Autosuggestibility Called Important Factor in Heart Disease
New Approach to Care of Infant Skin
Unique Cases of Pelvic Cancer Reported

The character of the services which the pharmaceutical advertiser offers to the medical profession is well represented by *Ciba Reports.* And this type of service is more and more in evidence as the pharmaceutical industry moves forward. The individual practicing physician now depends on the pharmaceutical advertiser for new information, for background material, and even for cultural stimulation. Hackneyed though the phrase may seem, pharmaceutical advertising serves the cause of medicine.

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Sources of Pharmaceutical Market and Economic Information

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The major sources of market and economic information on the pharmaceutical industry are discussed. An annotated bibliography, including all sources mentioned in this discussion and a number of supplementary sources, is appended to this paper.

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Statistics are important in the pharmaceutical industry. They form the basis for scientific research decisions, for medical research decisions, and for business decisions. As the pharmaceutical industry has become more complex, facts and statistical data likewise have become more useful. How quickly and efficiently the library is able to supply desired statistics is an excellent criteria of the quality of service offered by the industrial pharmaceutical library.

How many appendectomies were performed in the United States in 1952? What are the world-wide production figures on ergot, and which countries are the major growers? How many people will be over 65 in 1975? What is the incidence of amebiasis in the various countries of the world? What percentage of the United States production of penicillin in 1952 was exported to foreign countries? These are typical of the requests for statistical data that come into the industrial pharmaceutical library. Most frequently the answer to these requests are to be found in the standard statistical reference sources. Many times, however, these sources are not helpful, and it may be a reference in a textbook, a newspaper article, a printed speech, or perhaps an obscure leaflet issued by an advertising agency which has the answer. The librarian must be alert to these unusual sources, and he must carefully screen and index significant data contained in these sources.

This paper is concerned with the major sources of economic and market data as related to the pharmaceutical industry. The United States Government is the largest supplier of statistics on the pharmaceutical industry, but trade associations, trade journals, pharmaceutical companies, private research organizations, universities, and state governments also are important sources of statistical data.

Requests for current pharmaceutical economic and market data generally fall into one of these broad groups—production, consumption, foreign trade, new pharmaceutical products, prescriptions, disease incidence, mortality statistics, and financial and operating data on pharmaceutical industry.

Since it is impossible to discuss all the major sources of information in these fields, two or three important sources are mentioned in each category. A more extensive annotated list of sources has been compiled and is appended to this paper.

Production Statistics

Production statistics may be requested for individual chemicals or pharmaceutical preparations, for the total drug industry, or for the total United States production. Two key guides for production statistics are the U. S. Tariff Commission's annual report, *Synthetic Organic Chemicals, United States Production and Sales*, and the *Census of Manufactures*. The former publication gives production figures in pounds and quantity, value, and unit value sales statistics for synthetic organic chemicals and the raw materials from which they are made. Data for the report is supplied annually by more than 560 producing companies. The *Census of Manufactures* gives dollar value of shipments in finely divided subdivisions for biological products, inorganic and organic medicinal chemicals, and pharmaceutical preparations.

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Consumption Statistics

Consumption statistics for pharmaceutical products may be wanted for individual products, such as aspirin sales in 1952, or for the value of total drug products sold in a particular year. *Drug Topics*, one of the leading statistical reporting trade publications in the industry, also reports annually on drug sales and publishes a sales forecast. The report on drug store sales lists such items as vitamins, antihistamines, and eye lotions. The retail trade section of the *U. S. Census of Business* gives prescription, drug, and farm animal remedy statistics for drug stores.

Prescription Statistics

Statistics on prescriptions are one of the most often requested. Total prescription sales, average prescription price, sales of prescriptions by therapeutic use, and sales of individual prescription specialties are types of prescription data requested. *American Druggist*, a fortnightly trade publication, carries a continuing prescription survey in each issue. Prescriptions are classified by use and by major drug type. Twenty-six prescription types and eight drug types are listed. The *Associated Prescription Panel Service* is a monthly analysis of 33,500 prescriptions. This service gives data on the number of times prescription specialties were used in the prescriptions analyzed. The *National Prescription Survey*, a bimonthly publication of the Research Society averages 225,000 prescriptions per year. This survey gives such data as: number of one ingredient prescriptions, prescriptions by manufacturers, average prescription prices, and number of drug forms to fill specialty prescriptions. *Drug Topics* carries an annual prescription survey which is very useful.

New Pharmaceutical Specialties

Information on new pharmaceutical specialties, while not in the area of statistics, is closely related to this field. Requests for information on trade and chemical names of pharmaceutical specialties, their content, and use are frequently requested. Many excellent publications of this type are available. The *Modern Drug Encyclopedia* gives comprehensive data on prescription specialties in the United States. For quick identification of specialties the *American Druggist Blue Book* and the *Drug Topics Red Book* are very useful. *Facts and Comparisons* lists together products of similar therapeutic use, and it is useful for this purpose, as well as for quick identification of specialties. *Unlisted Drugs*, a notable cooperative publication of industrial pharmaceutical librarians belonging to the Special Libraries Association, lists foreign as well as domestic drugs. It gives trade and chemical names and the action and dosage of specialties listed. A very useful feature of this publication is the listing of literature references which are given for each specialty.

Statistics on Scope of Pharmaceutical Market

Statistics related to the scope of the market for pharmaceutical preparations may require data on the incidence of disease, population figures, or mortality figures. Population data such as age, sex, marital status, race, major occupation groups are found in the *Census of Population*. The *Current Population Reports* which supplement and bring up to date the *Census of Population* are issued in several series. Estimates of total U. S. population, population by states, school enrollment, and the labor force are reported at irregular intervals.

Vital Statistics of the United States is the most important source for mortality statistics. Deaths from 254 selected causes by race and sex for the United States and each state are given. Supplementing this report is the *Monthly Vital Statistics Report*, which contains mortality data for 43 causes of death. The *Communicable Disease Summary* and *Morbidity and Mortality* carry weekly summaries on the number of cases of more than 20 diseases during the previous week. *Public Health Reports* frequently carry review-type articles on specific diseases in which comprehensive statistical data on the incidence of diseases are discussed. The *Statistical Bulletin of the Metropolitan Life Insurance Company* contains a monthly summary of death rates per 100,000 policyholders from selected causes. Special surveys of specific diseases are regularly featured in which comprehensive statistical data are generally included.

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Foreign Trade Statistics

Import and export statistics are championed by the Department of Commerce's publications *United States Imports of Merchandise* and *United States Exports of Merchandise*. Statistics on the amount of crude drugs imported into the United States or the export of finished pharmaceuticals are listed in these publications. Another very useful, but somewhat outdated publication is the U. S. Tariff Commission's *Summaries of Tariff Information*. In addition to import statistics on the foreign value, unit value, quantity, and tariff rates on pharmaceutical preparations, informative, general discussions are included for each product listed. Discussions include information on countries which are leading producers, general information on the product, foreign capacity, prices, and others.

Drug Store Statistics

Statistical information on drug stores, the industry's chief outlet for its products, is broad in scope. Location and number of drug stores, sales, sales per United States family, drug sales by city, inventories, drug store failures, wholesale prices of pharmaceuticals, drug store profits and margins are typical of the statistical data requested in this field. The *Monthly Retail Trade Report, Survey of Current Business, Business News Reports* and the sales management *Survey of Buying Power* are all publications of interest for statistical data on drug stores.

Financial and General Data on Pharmaceutical Companies

Financial and general statistics available on pharmaceutical companies and the industry as a whole are readily available. Moody's Services and Standard & Poor's Services supply data on the history, capital structure, commerce share earnings, dividends, income, inventory turnover, price earnings, and ratios on the individual pharmaceutical companies. The *Monthly Labor Review* contains statistics in each issue on the number of employees in the drug industry, monthly labor turnover rates, and hours and gross earnings of production workers. The *Census of Manufactures* includes statistics on number of employees, wages, value of products. Data are presented for the pharmaceutical industry as a group and separately, by geographic divisions and of states.

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List of pharmaceutical specialties available in the United States. Prices and form of product are included.

(3) *Associated Prescription Panel Service, Collaborator Report.* Monthly. Market Research Associates, Darien, Conn.
Prescription analysis of 33,000 prescriptions per month. Data on the number of times prescription specialties were used out of total prescriptions analyzed.

(4) *Business News Report.* Monthly. U. S. Department of Commerce, Washington, D. C.
Retail store sales section gives monthly sales of drug and proprietary stores. Wholesalers' sales and inventories section gives monthly estimated wholesale sales and inventories of drugs and sundries.

(5) "Census of Business, 1948." 7 volumes. 1951–52. U. S. Department of Commerce, Washington, D. C.
Retail trade, vol. 1–3. Commodity sales, inventories, employment payroll of drug stores.
Wholesale trade, vol. 4–6. Basic statistics on wholesale trade including drugs (general line) and drugs and drug sundries, showing operating expenses, payrolls, commodities sold, size of establishments, classes of customers, organization, and others.

(6) "Census of Manufactures, 1947." 3 volumes and supplement. 1950. U. S. Department of Commerce, Washington, D. C.
General summary, vol. I. Gives general statistics on size, personnel, type of organization, and so forth, for the drug industry.
Statistics by industry, vol. II. Statistics cover such subjects as the number of establishments, wage earners, wages, cost of materials, value of

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products, and value added by manufacture. Data are presented for industry as a group and separately, by geographic divisions and by states. Statistics by states, vol. III. Detailed statistics on number of establishments making drugs and medicines, employees, value of products, percentage of value represented by cost of materials and manufactures for each of the 48 states, the District of Columbia, Alaska, Hawaii, in all counties and cities of more than 10,000 inhabitants.
Product supplement. Quantity and value of shipments of more than 6000 products manufactured by U. S. industry.

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Number of inhabitants, vol. I. Total population for states, counties, rural areas, etc.
Characteristics of the population, vol. II. Sex, age, race, nativity, major occupation group, industry group, and others.
Labor force, vol. III.
Characteristics by age, vol. IV.

(8) *Chemical Economics Handbook.* Annual. Stanford Research Institute, Palo Alto, Calif.
Statistics and charts on all chemicals of commercial importance and data on hundreds of companies.

(9) *Chemical Facts and Figures.* Annual. Manufacturing Chemists' Association, Washington, D. C.
A handy compilation of government and other statistics on production and consumption indexes, hours and earnings, financial and tax data, foreign trade, wholesale price indexes, and others.

(10) *Chemical Market Report.* Monthly. Foster D. Snell, Inc., New York.
An index and summary of significant published data in trade journals, government publications, scientific journals, and house organs in the field of chemical marketing, research, supply, and development.

(11) *Chemical and Rubber Industry Report.* Monthly. U. S. Department of Commerce, Washington, D. C.
Gives monthly production figures for United States production of antibiotics, sulfonamides, and vitamins.

(12) *Current Population Reports.* U. S. Department of Commerce, Washington, D. C.
Current estimates of population by state, age, sex, and marital status. Several series are published at various times.

(13) *Drug Topics.* Biweekly. Topics Publishing Co., New York.
Includes annual surveys of what the public spends for health goods bought through drug stores; the vitamin market; first aid goods department; prescription census; and forecast of trend of sales, prices, stocks, gross margins, and others.

(14) *Drug Topics Red Book.* Annual. Topics Publishing Co., New York.
List of pharmaceutical specialties available in the United States. Prices and form are included.

(15) *Drug Trade News.* Biweekly. Topics Publishing Co., New York.
Publishes annual analysis of the financial statements of pharmaceutical companies.

(16) *Dun's Statistical Review.* Monthly. Dun & Bradstreet, New York.
Monthly statistics on the number of drug store failures and their current liabilities.

(17) *Economic Almanac.* Biannual. National Industrial Conference Board, New York.
A statistical compilation, including population, consumption, and manufacturing data.

(18) *Ethical Drug Audit.* Quarterly. Dun & Bradstreet, New York.
Data on the market position of producers of specified prescription specialties; market position, by classification of the market for specialties; percentage distribution of purchases among various classifications of the market. Data on product, form, volume, and strength of specialty.

(19) *Facts and Comparisons.* 314 pages. 1953. Monthly revisions. Facts and Comparisons, Inc., St. Louis, Mo.
List of pharmaceutical specialties available in the United States. Products of like nature are arranged together. Content, dosage, and price given.

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(21) *Federal Reserve Bulletin.* Monthly. Federal Reserve System, Washington, D. C.
Statistics on wholesale prices of drugs and pharmaceuticals.

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Contains informational articles on drugs and pharmaceuticals and industrial developments in foreign countries.

(23) *Foreign Commerce Yearbook.* Annual. U. S. Department of Commerce, Washington, D. C.
Contains import and export statistics, including the value and amounts of pharmaceuticals from and to the United States and the principal countries of the world.

(24) *Hayes Druggists Directory and Commercial Reference Book.* Annual. E. N. Hayes, Detroit, Mich.
Retail druggists with their financial standing and credit rating; drug wholesalers; drug chains; department stores having a full drug and toiletgoods departments.

(25) *Lilly Digest.* Annual. Eli Lilly and Co., Indianapolis, Ind.
Statistics on drug store costs, margins, profits, prescription prices, and refills.

(26) *Medical Marketing.* Monthly. Medical Economics, Inc., Rutherford, N. J.
Contains annual physician survey on prescribing habits, dispensing trends, patient load, working load, and time spent per patient.

(27) *Modern Drug Encyclopedia.* 5th ed., 1952. Quarterly supplements. Drug Publications, New York.
List of pharmaceutical specialties available in the United States. Chemical name, action and uses, administration, and supply data given.

(28) *Modern Medicine 1953 Prescription Sales Marketing Guide by States and Counties.* 1953. Modern Medicine Publications, Minneapolis, Minn.
N.W.D.A. trade areas, prescription drug store population estimated prescription sales, and so forth.

(29) *Modern Medicine Topics.* Monthly. Modern Medicine, Minneapolis, Minn.
Statistical reports on incidence of diseases, physicians, prescriptions, and others.

(30) *Monthly Labor Review.* Monthly. U. S. Department of Labor, Washington, D. C.
Statistics on number of employees in drug industry; monthly labor turnover rates; hours and gross earnings of production workers.

(31) *Monthly Retail Trade Report.* Monthly. U. S. Department of Commerce, Washington, D. C.
Gives statistics on estimated monthly sales of retail stores, including drug stores; percentage change in sales of retail stores, including drug stores.

(32) *Monthly Vital Statistics Report.* Monthly. U. S. Department of Health, Education, and Welfare, Washington, D. C.

(33) *Monthly Wholesale Trade Report.* Monthly. U. S. Department of Commerce, Washington, D. C.
Statistics on drug wholesalers' sales and inventories; geographic division included.

(34) Moody's Services. New York.
Manual of Investments, Industrials. Annual and semiweekly. Gives data on history, capital structure, subsidiaries, business and products, income accounts, financial and operating data, and capital stock for the individual companies.
Stock Survey. Weekly. Frequent financial review of the industry and data on individual companies.

(35) *Morbidity and Mortality.* Weekly. U. S. Department of Health, Education, and Welfare, Washington, D. C.
Statistics on cases of specified diseases with comparative data in the United States.

(36) *National Prescription Audit.* Bimonthly. Research Society, Boston, Mass.
Analysis of 225,000 prescriptions per year. Data on per cent of prescriptions, per cent dollar volume, average prescription prices, pieces of direct mail, and new products of prescriptions analyzed. Number of different drug forms to fill specialty prescriptions, number of one ingredient prescriptions, and ingredient of prescriptions by manufacturers are also given.

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Record of conditions and prices in industrial markets for chemicals and drugs.

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An audit of the invoices of 800 drug stores of drug and pharmaceutical products. Data are projected into national totals, and broken down by territories, county sizes, and store types.

(39) *Sales Management Survey of Buying Power.* Annual. Sales Management, New York.
Statistics on drug store sales per U. S. family by states; drug store sales for 200 leading counties; estimated retail drug sales by city; county, metropolitan areas, and states. Data for Canada also included.

(40) Standard and Poor's Services. New York.
Listed Stock Reports. Quarterly. Financial analysis for individual companies. Data on common share earnings, dividends, income, capitalization, and others.
Industry Surveys, Drugs and Cosmetics, Basis Analysis. Annual. Financial analysis of the industry. Data on sales records, inventory turnover, profit margins, dividend policies, and price-earnings ratios for the industry. Income account and balance sheet statistics for individual companies since 1939.
Industry Surveys, Drugs, and Cosmetics, Current Analysis. Quarterly. Abbreviated, but more current, report on the industry. Contains data similar to that found in *Basic Analysis* report.
Corporation Records. Continuous revisions. Factual data on pharmaceutical companies and their securities. Gives corporate background information, stock data, and earnings and financial data.

(41) *Statistical Abstract of the United States.* Annual. U. S. Department of Commerce, Washington, D. C.
Statistics from various sources on drugs and druggists preparations, which include cost of material used in production, value of manufacture, indexes of employment and payroll, average hours and earnings of employees, corporation income tax returns, excise taxes, and foreign trade. Also statistics on trade of drug stores; wholesale prices for medicinal and pharmaceutical preparations, and expenditures by states for health and sanitation.

(42) *Statistical Bulletin of the Metropolitan Life Insurance Co.* Monthly. The Company, New York.
Monthly tabulation of death rates per 100,000 policyholders from selected causes. Includes special surveys of disease incidence of all types.

(43) *Summaries of Tariff Information. Vol. 1, Chemicals Oils, and Paints. Part 1, Noncoal-tar Acids, Alcohols, Resins, and Medicinals.* 1948. U. S. Tariff Commission, Washington, D. C.
Import statistics on medicinal and pharmaceutical preparations. Foreign value, unit value, quantity, and tariff rates.

(44) *Survey of American Listed Corporations: Data on Profits and Operations.* Annual. U. S. Securities and Exchange Commission, Washington, D. C.
Includes data on the drug industry and drug stores.

(45) *Survey of Current Business.* Monthly. U. S. Department of Commerce, Washington, D. C.
Contains monthly statistical data on employment and wages, production and distribution, retail sales of drug stores, and an index of wholesale drug prices.

(46) *Synthetic Organic Chemicals.* Annual, with monthly supplements. U. S. Tariff Commission, Washington, D. C.
Gives U. S. production and sales of intermediates and finished organic chemicals, by groups.

(47) *United States Imports of Merchandise for Consumption in Commodity by Country of Origin Arrangement.* **FT410.** Monthly and annual. U. S. Department of Commerce, Washington, D. C.
Lists industrial commodities, the total imported from all countries, and for each commodity information on the amount of each country from which imports are $10,000 or more.

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List of recently introduced domestic and foreign drug specialties. Gives chemical name, action, dosage, and literature reference for each specialty cited.

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Part I. Natality, marriage, divorce, morbidity, and life table data for the United States.
Part II. Natality and mortality data for the United States, by place of residence.

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Biochemical, Pharmacological, and Medical Terminology in French and German Chemical Literature

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As a guide to the literature chemist who may be called upon to translate or abstract biochemical, pharmacological, and medical literature, the following subjects are discussed: pharmaceuticals of chemical origin; a basic anatomical and pathological vocabulary in French and German; "aliases" under which many chemical substances are known in pharmacology and medicine; words whose literal meaning differs from their pharmacological, biochemical, and medical connotations; and a general method of approach to such literature. Listed are frequently used therapeutic preparations with their French and German equivalents, helpful English and foreign-language reference works, and the Latin and Greek prefixes and suffixes most prevalent in medical terminology.

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The purpose of this paper is to present suggestions to the literature chemist who has a reading knowledge of chemical French and German and who may be called upon to translate or abstract biochemical, pharmacological, or medical material in these languages.

Many chemical substances have been and are being widely used in medicine. In fact, chemotherapeutic agents have come to occupy an increasingly important place in modern medicine. Their physiological action and the therapeutic benefits derived from them are of more than theoretical interest to the manufacturing chemist. Any description of their physical and chemical properties is likely to be accompanied by a discussion of their effects on the human organism. The literature chemist may consequently have to translate or abstract reports of experimental investigations and clinical trials in which the therapeutic applicability of both old and new chemical substances has been tested. Chemical companies are concerned with the toxicity of many of the chemicals they manufacture, even if these are not used in human medicine, because these substances may be responsible for occupational diseases and consequently affect the health of those handling them.

The approach to medical material is essentially the same as the approach to other scientific texts. The primary nonlinguistic prerequisite for translating scientific material is some knowledge of the subject matter involved *(1)*. Because all cannot be expected to have specialized knowledge in the fields of medicine and pharmacology, the question arises as to where the necessary basic information can be found in ready reference form.

Reference Works

In addition to a large number of excellent medical dictionaries, many of which are listed in Table I, reference should also be made to English-language textbooks and manuals intended for the physician. Before translating a given medical text, it may be well to consult such works in order to acquire some background knowledge of the physiological, bacteriological, or pathological concepts discussed.

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

An excellent all-purpose reference in English is "The Merck Manual of Diagnosis and Therapy" which, when used in conjunction with a foreign-language handbook, such as the "Formulaire Astier" in French, will answer most terminological problems. Another useful reference, particularly for clinical bacteriology and histology, is the Department of the Army's technical manual entitled "Methods for Laboratory Technicians," prepared under the direction of the Surgeon General. Among the pharmacological references frequently worth consulting is "The Merck Index of Chemicals and Drugs," which also lists some foreign pharmaceutical preparations, although perhaps not enough, and contains many valuable tables for converting measures and weights, pH determinations, radioactive isotopes, coal-tar dyes for drugs, boiling temperatures of liquids, and melting points. Incidentally, body weights and temperatures should, as a rule, be converted from the metric and centigrade systems, but measurements in laboratory data should not. Other indispensable source references for French, Belgian, Swiss, German, Austrian, and other foreign proprietary drugs are the "United States Pharmacopeia," "New and Nonofficial Remedies," and similar treatises on drugs, their formulas, and methods of preparation published abroad. The names of some chemotherapeutic agents, proprietary or otherwise, may not be readily recognizable in French or German because of their orthographic adaptation to these languages.

Table II is a list of some of the major types and categories of therapeutic agents in use today, with French and German equivalents, and a necessarily brief identification of the physiological action involved. This tabulation does not include those categories of therapeutic agents which are used in the treatment of a specific disease (antisyphilitics, antimalarials, antitetanics, etc.), or those belonging to a family of chemotherapeutic agents (barbiturates, arsenicals, sulfa drugs, etc.).

Another problem frequently encountered in translating or abstracting pharmaceutical material is that many chemical substances known to the chemist by one nonproprietary name are known to the pharmacologist by another. However legitimate these "aliases" may be, they make for confusion. To cite three from a list that would fill a fair-sized book: The anesthetic "cyclopropane" has also been called "trimethylene"; the systematic name of "methylal," or "formal," is "dimethoxymethane"; and "hyoscine" is a synonym of "scopolamine," the optically inactive variety of which is also called "atroscine." Most of the pharmaceutical reference works mentioned above list both the pharmacological and chemical names of these dual-name substances.

A somewhat similar plurality of nomenclature also exists in the field of pathology, in view of the fact that most diseases have at least two names: the eponymic name—i.e., that of the physician or bacteriologist who first described the condition or isolated the etiological agent involved—and the descriptive name. Not infrequently, a disease may even have several descriptive names. "Hodgkin's disease," for example, the French and German equivalents of which are *maladie de Hodgkin* and *Hodgkins Krankheit*, is also known as "infectious granuloma," "malignant granuloma," "malignant lymphoma," "lymphosarcoma," and "pseudoleukemia." In French medical texts, it may be referred to as *lymphogranulomatose maligne, granulomatose maligne*, or *adénie éosinophilique prurigène*, and in German it can also be called *Pseudoleukämie, malignes Granulom*, or *Lymphogranulomatose*. The blame for this terminological confusion, or at least for what strikes the lay translator as such, cannot in all fairness be laid at the door of those who compile medical dictionaries, some of whom—like Pierre Lépine of the Pasteur Institute—are eminent medical men, as they understandably and rightly wish to avoid being charged with the sin of omission and consequently feel that they should include all known names (however obsolete or obsolescent). A desirable approach to this problem is to call the disease by the name under which it is listed in English reference works on pathology or in such general medical references as the "Merck Manual of Diagnosis and Therapy."

A number of pathological conditions in English have retained the original French, German, or other foreign name. Thus, the form of epilepsy in which there are severe convulsions and loss of consciousness is known in English as *grand mal;* the mild form, in which vertiginous or other sensations take the place of convul-

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Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

sions, is called *petit mal.* Such designations should not be translated. A rather curious condition, to cite an example from German, is *Witzelsucht,* also known as such in English. This is the designation for a psychopathological condition marked by the making of poor jokes and puns and the telling of pointless stories, at which the patient is himself intensely amused.

As in English, a number of medical terms in both German and French have a chameleonlike quality; their meaning changes with the context. Thus, *Blase* can refer to "bladder," "vesicle," or "blister," depending on whether the context suggests anatomy, embryology, or pathology. *Kreuzung* means "hybridization" in biology and "decussation" or "chiasma" in neurology. In surgery, *Schnitt* is an "incision," but in histology it is a "section" or a "slide." When used in an anatomical sense, *Zäpfchen* means "uvula," but in pharmacology it means "suppository." In the one field of anatomy alone certain terms will have different English equivalents, depending on the part of the body involved. *Kammer* denotes both the "ventricle" of the heart or brain and the "chamber" of the eye. *Bein* is generally "leg," although it frequently refers to "bone," especially in combining forms. In dermatology, *Lederhaut* is the German word for the "corium," or "true skin," but in ophthalmology it refers to the "sclerotic coat" of the eye. An example from German which has two almost antithetical meanings is *Herzschlag.* In physiology, it means "heartbeat," but in pathology it refers to "cardioplegia," or paralysis of the heart—obviously a difference not to be taken lightly.

The term *Beschwerden,* which is frequently used in German clinical case histories, will only occasionally be correctly translatable as "complaints." In most instances it has the weight of what an English medical writer would call "subjective symptoms" or just "symptoms." And no matter how difficult or annoying a German text may be to decipher, *Halsweh* is nothing more than a "sore throat" and should not be rendered as "pain in the neck."

French medical terminology also contains a number of terms which do double or even triple duty. *Ampoule* is an "ampoule" to the pharmacist or laboratory technician; but to the pathologist it is a "blister" or a "vesicle." *Loupe* is a "magnifying glass" in the field of optics; in pathology it denotes a "sebaceous cyst" or "atheroma." In pharmacology, *pilon* is a "pestle" or "stamper"; in orthopedics, it is the French term for an "artificial leg." In a chemical text *tampon* is the equivalent of "buffer," but in therapeutics it means "pledget," "tampon," or "swab." Finally, *tourniquet* is the term for the instrument used for the compression of a blood vessel, and as such it has the same meaning in English. As a pathological condition, however, it is one of the French names for what we call "Gerlier's disease" or "endemic paralytic vertigo." A general French expression which is widely used in case-history descriptions is *au niveau de,* as in the phrase: "Le malade avait une inflammation au niveau des articulations." This should not be translated literally as an "inflammation at the level of the joints," but simply as an "inflammation of the joints."

In the preface to his "Dictionary of New Medical Terms," first published at the turn of the century, George M. Gould wrote:

> Our modern language of medicine is unique in that it is made up of the unchanged and undigested materials and relics used or contributed during its entire history. The persisting substratum is Latin, upon which has been placed a mass of pseudo-Greek words not physiologically created nor grown by natural philologic methods, but springing Minerva-like from the brains of thousands of modern Jupiters. These largely bear the marks of their parentage in characteristics that do not, or should not, beget a spontaneous pride of lineage.

Gould then says:

> From a highly variegated medievalism that has, indeed, never ended, we have taken over another unassimilable conglomerate, and superadded are thousands of dissimilar terms derived from modern chemistry, biology, bacteriology, and many other sciences. . . . The result is before us: a huge and unassimilated philologic mass, many times greater than it should be, the despair of medical students and of makers of dictionaries.

And Gould might have added, especially of translators, who must grapple with this "philologic mass" twice: first in the foreign language and then in English. R. J. E. Scott in the preface to the first edition of this dictionary, suggested that

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"scientists, when about to assume the role of parents of new words, should, whenever necessary, seek the aid of the man with a knowledge of Greek, rather than undergo (without the help of a specialist) the pangs of etymologic labor, with the resulting birth of a linguistic monstrosity."

This, therefore, is the problem we have inherited. The key to its solution—for those called upon to decipher foreign biochemical, pharmacological, and medical texts—lies in the fact that about a third of the medical terminology in German and well over half the medical vocabulary in French is of Greek or Latin derivation, this percentage being much higher for the strictly scientific element. There was a time, not so long ago, when the study of Latin, if not also of Greek, was a prerequisite for the study of medicine. Today this is no longer universally the case, but some familiarity with these two far from dead languages will obviously simplify the task of acquiring a basic biochemical, pharmacological, and medical vocabulary, not merely in English but also in German and especially in French. But, to quote from Lloyd W. Daly's "Fundamentals of Medical Etymology" (part of the "American Illustrated Medical Dictionary"), "since it no longer seems economical to learn to read the two languages for this purpose, some short cut to the necessary information is needed, and again experience has shown that certain fundamentals of vocabulary and linguistic principle can easily be mastered and are of great assistance."

Such a short cut is offered in the analytical word lists included in most medical dictionaries today. One of the most complete lists of Latin and Greek prefixes, suffixes, and combining forms entering into the composition of modern English medical terminology will be found in the "Fundamentals of Medical Etymology."

Table III is based on various source references, chiefly "Webster's New International Dictionary," 2nd ed., G. & C. Merriam Co., Springfield, Mass., 1953; "American Illustrated Medical Dictionary"; "Gould's Medical Dictionary"; E. Veillon, "Medical Dictionary", Hans Huber, Bern, 1950; "Dictionnaire Polyglotte des Termes Médicaux"; and others (see list of medical reference works cited). The derivative Greek or Latin words themselves are not given following each entry, although their pertinent English meaning or meanings are provided, and in some cases this is followed by an appropriate explanation of how the prefix or suffix is generally used in biochemical and medical terms. Finally, an example is given to illustrate use of the combining form in both a German and a French compound derivative.

In view of the fact that there is as yet no agreement on the use of the German consonants *c*, *k*, and *z* in the spelling of many foreign terms of Greek and Latin origin, many prefixes, combining forms, and suffixes normally written with *c* in English and French are frequently written with *k* or *z* in German. Thus, *Antibioticum* is written with either *c* or *k* and *Leukocytose* can be written with either *z* or *c*. Generally speaking, Swiss and Austrian journals prefer the Latin *c*, in both the singular and the plural; German journals tend to favor the *k*. In Table III, however, these alternative spellings have not been entered. For German medical words of Greek or Latin origin written with a *k* or *z*, therefore, the pertinent prefix, combining form, or suffix will be found spelled with *c*. Many of the more obvious medical prefixes and combining forms, such as "pharmaco-," "psycho-," "sanguino-," "musculo-," and "pulmo-," have not been listed.

Many related terms are derived from both the Latin and the Greek word for a given concept. Thus, *cancérigène* comes from the Latin word for cancer and *carcinomateux* from the Greek word for cancer; *Ovogenese* comes from the Latin word for egg and *Oogenese* from the Greek word for egg.

Conclusion

When he undertook to prepare this paper, the author developed what in retrospect he would diagnose as a mild case of mental onychophagia, not because of any latent lalophobia when addressing a select audience, but rather because of a congenital condition of periodic logagraphia and chronic ergophobia—a serious syndrome, and one which reflects the highly infectious nature of the subject matter. What is meant is that when first faced with the prospect of having to work out this paper he was mentally biting his fingernails (onychophagia), not because of any extreme dislike for public speaking (lalophobia), but because of a periodic inability to express ideas in writing (logagraphia) and a morbid dread of work (ergophobia).

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However, if he has succeeded in assembling material that may be of some help in translating or abstracting French and German medical texts, he will derive considerable comfort from the fact that the above syndrome, serious as it is, may yet allow a favorable prognosis.

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* These references are especially recommended because of their comprehensiveness, reliability, and general usefulness.

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Table II. Major Categories and Types of Therapeutic Agents and Their French and German Equivalents

This list does not include categories of therapeutic agents which are used in the treatment of a specific disease (antisyphilitics, antimalarials, antitetanics, etc.), or those belonging to a family of chemotherapeutic agents (barbiturates, arsenicals, sulfa drugs, etc.). For reasons of space, German compound words ending in *-mittel* (agents) are here abbreviated to -m., and the noun *Mittel*, to M.

Abortifacients	abortifs; Abtreibungsm.	causing abortion
Absorbents or absorbefacients	absorbants, résorbants; Absorbentia, Resorbentia	promoting absorption
Activators	substances d'action; Aktionsstoffe	rendering another substance active
Adjuvants	adjuvants; Adjuventen, Hilfsm.	assisting other remedies
Adrenolytics	andrénolytiques; adrenolytische M.	inhibiting action of adrenergic nerves
Alteratives	modificateurs; umstimmende M.	re-establishing healthy functions
Analeptics	analeptiques; Analeptica	stimulating central nervous system
Analgesics	analgésiques; Analgetica, Schmerzstillungsm.	relieving pain
Anaphrodisiacs	anaphrodisiaques; Anaphrodisiaca, geschlechtsvermindernde M.	repressing sexual desire
Anesthetics	anesthésiques; Anaesthetica, Betäubungsm.	causing insensibility
Angiotonics	angiotoniques; Blutdruckerhöhende M.	increasing vascular tension
Anhidrotics or antihidrotics	anhidrotiques; Anthidrotica	checking sweat secretion
Anodynes	calmants; Linderungsm.	relieving pain
Antacids	antiacides; säurebindende M.	counteracting acidity
Antalgics or Antalgesics	antalgiques; Antalgica, Schmerzstillungsm.	relieving pain
Antemetics	antiémétiques; Antemetica	relieving nausea, vomiting
Antibiotics	antibiotiques; Antibiotica	destroying bacteria
Anticatalysts	anticatalysateurs; Antikatalysatoren	retarding catalyzer action
Anticoagulants	anticoagulants; Antikoagulantien	delaying blood coagulation
Anticonvulsants	anticonvulsifs, anticonvulsivants; krampflösende M., Spasmolytica	acting against convulsions
Antidiarrheals	antidiarrhéiques; Antidiarrhoica	counteracting diarrhea
Antidiuretics	antidiurétiques; Antidiuretica	checking urinary secretion
Antidotes	antidotes; Antidoten, Gegenm., Gegengifte	counteracting a poison
Antiferments	antiferments; Antifermente	preventing fermentation
Antigens	antigènes; Antigene	inciting antibody formation
Ant(i)helminthics	antihelmintiques, anthelmintiques; Wurmm., Anthelminthica	destroying worms
Antihemolytics	antihémolytiques; antihemolytische M.	preventing hemolysis
Antihemorrhagics	antihémorragiques; blutstillende M.	stopping hemorrhage
Antihistaminics	antihistaminiques; Antihistamine, Antihistaminstoffe	counteracting histaminic action
Antiparasitics	antiparasitaires; Antiparasitica	destroying parasites
Antiphlogistics	antiphlogistiques; Antiphlogistica	reducing inflammation or fever

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Antipruritics	antiprurigineux, antiprurigineux; jucklindernde or juckstillende M.	relieving itching
Antipyretics	antipyrétiques; Fieberm., Antipyretica	reducing fever
Antiseptics	antiseptiques, stérilisants; Antiseptica	inhibiting bacteria and preventing putrefaction
Antispasmodics	antispasmodiques; Spasmolytica, krampflösende M.	relieving spasms or convulsions
Antisudorifics	antisudoraux; schweisslindernde M.	checking excessive sweating
Antithermics	antithermiques; Antithermica	cooling agents
Antitoxins	antitoxiques, contrepoisons; antitoxische M.	counteracting toxins
Antitussives	*See* "Bechics"	
Antivenoms or antivenins	antivenimeux, antivénéneux; Gegengifte	counteracting snake venom
Aperients	purgatifs légers; eröffnende M.	mild purgatives
Aperitives	apéritifs; Aperitiva, appetitanregende M.	stimulating appetite
Aphrodisiacs	aphrodisiaques; Aphrodisiaca	exciting sexual impulse
Arcana	arcanes; Geheimm.	secret medicines, or nostrums
Aromatics	aromatiques; Aromatica, aromatische M.	stimulants with spicy odor
Astringents	astringents; Adstringentia	causing contraction and arresting discharges
Bactericides	bactéricides; bakterizide M.	destroying bacteria
Bacteriolytics	bactériolytiques; bakteriolytische M.	dissolving bacteria
Bacteriostatics	bactériostatiques; bakteriostatische M.	arresting bacteria growth or multiplication
Bechics	béchiques; Hustenm.	cough remedies
Bronchodilators	bronchodilatateurs; Luftwegeerweiternde M.	expanding lung air passages
Cardiotonics	cardiotoniques, tonicardiaques; Cardiotonica, Herzm.	strengthening heart action
Carminatives	carminatifs; Carminativa, Blähungsm., windtreibende M.	relieving flatulence
Catalytics	catalysateurs, catalyseurs; Katalysatoren, Kontaktstoffe	causing catalysis
Cathartics	cathartiques; Kathartica	causing purgation
Caustics	caustiques; Ätzm.	corroding, burning, destroying living tissue
Cholagogues	cholagogues; Cholagoga	stimulating bile flow
Choleretics	cholérétiques; gallentreibende or gallensekretionsfördernde M.	*See* "Cholagogues"
Contraceptives	anticonceptionnels; konzeptionsverhütende M.	preventing conception
Convulsants	convulsifs; krampferregende M.	causing convulsions
Cordials	cordiaux; herzstärkende M.	stimulating heart action
Cosmetics	cosmétiques; Hautm.	beautifying agents
Decongestives	décongestionnants; blutandrangverhindernde M., schleimhautabschwellende M.	reducing congestion
Demulcents	adoucissants; mildernde or erweichende M., Linderungsm.	soothing irritation or abraded surfaces
Deodorants	désodorisants; Desodorantia	removing offensive odors
Depilatories	dépilateurs; Enthaarungsm.	removing hair
Depressants	dépresseurs; depressorische or herabstimmende M.	diminishing functional activity

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Derivatives	dérivatifs, révulsifs; ableitende M.	producing derivation or withdrawing blood from seat of disease
Desensitizers	désensibilisants; Desensibilisierungsm.	depriving of sensation
Desiccants	dessicatifs; Desikationsm., Austrocknungsm., austrocknende M.	promoting dryness
Detergents	détersifs; Detergentia	cleansing agent
Diaphoretics	diaphorétiques; Diaphoretica, Schwitzm., schweisstreibende M.	stimulating perspiration
Digestives or digestants	digestifs; verdauungsfördernde M.	stimulating digestion
Disinfectants	désinfectants; Desinfektionsm.	freeing from infection
Ecbolics	ecboliques; Wehenm.	producing uterine contractions
Emetics	émétiques, vomitifs; Emetica, Brechm.	causing vomiting
Emmenagogues	emménagogues; Emmenagoga	stimulating menstrual flow
Emollients	émollients; mildernde or erweichende M.	softening, soothing agents
Emulgents	émulgents; emulgierende M.	stimulating bile/urine flow
Epilators	épilatoires; Enthaarungsm.	removing hair
Epispastics	épispastiques; Hautreizm.	blistering agents
Errhines	sternutatoires; Niesm.	promoting nasal discharge
Escharotics		*See* "Caustics"
Excipients	excipients; formgebende M.	conferring suitable prescription consistency when added
Excitants	excitants; Reizm.	producing functional or cerebral excitation
Expectorants	expectorants; Expektorantien	stimulating expulsion of mucus, etc., by spitting
Febrifuges	fébrifuges; Febrifuga, Fieberm.	reducing fever
Fixatives	fixateurs; Fixateure, Fixierungsm.	fixing agents used in histologic or pathologic specimen preparation
Fungicides	fongicides; fungicide M.	destroying fungi
Galactagogues	galactagogues; Galactagoga, Lactagoga	increasing milk secretion
Germicides	germicides; keimtötende M.	destroying germs
Hematopoietics	hématopoïétiques; blutbildende or hämatopoetische M.	promoting formation of blood
Hemostatics	hémostatiques, hémostyptiques; Hämostyptica	arresting flow of blood
Hydragogues	hydragogues; Hydragoga	producing watery discharge, especially from the bowels
Hypertensors	hypertenseurs; blutdruckerhöhende M.	increasing blood pressure
Hypnagogues	hypnagogues; Hypnagoga, einschläfernde M.	inducing sleep or drowsiness
Hypnotics	hypnotiques, somnifères, narcotiques; Schlafm., Betäubungsm.	inducing sleep
Hypotensors	hypotenseurs; blutdrucksenkende M.	lowering blood pressure
Inhalants	inhalants; Inhalationsm.	medicines to be inhaled
Inhibitors	inhibiteurs; Hemmstoffe	suppressing or restraining an action
Insecticides	insecticides; insektizide M.	destroying insects
Irritants	irritants; Reizm.	inducing irritation

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Keratolytics	kératolytiques; keratolytische M.	producing keratolysis
Lactifuges	produits antilaiteux; Milchabsonderung vermindernde M.	checking milk secretion
Laxatives	laxatifs, purgatifs; Laxative, Laxierm., Abführm.	loosening the bowels
Lenitives	lénitifs, calmants, sédatifs; Linderungsm.	demulcent, mildly cathartic agents
Miotics or myotics	myotiques; Myotica, pupillenverengernde M.	causing pupil contraction
Mydriatics	mydriatiques; Mydriatica, pupillenerweiternde M.	dilating the pupil
Narcotics	narcotiques, stupéfiants; Narcotica, Rauschgifte, Betäubungsm.	producing sleep or stupor
Nervines or nerve tonics	nervins, sédatifs; Nervenm.	allaying nervous excitement
Obtundents		*See* "Demulcents"
Oxytocics	oxytociques, ecboliques; Ocytocica, Wehenm.	hastening childbirth
Palliatives	palliatifs; Palliativm.	affording relief, but not cure
Panaceas	panacées; Allheilm.	cure-alls
Parasiticides	parasiticides; parasiticide M.	destroying parasites
Parasympath(ic)o-mimetics	parasympathicomimétiques, vagomimétiques; parasympathikomimetische M., parasympathikuserregende M.	producing effect resembling stimulation of parasympathetic nerves
Parturifacients	agents provoquant la parturition; Entbindungsm.	inducing or facilitating childbirth
Patent medicines	spécialités pharmaceutiques; Patentmedizine	drugs protected by patent
Pectorals	calmants la toux; hustenstillende M.	cough or chest disease remedies
Prophylactics	préventifs, prophylactiques; Vorbeugungsm., Präventivm., Schutzm.	tending to ward off disease
Ptarmics		*See* "Errhines"
Ptyalogogues	ptyalogogues; Ptyalagoga	*See* "Sialogogues"
Purgatives	purgatifs; Abführm.	causing bowel evacuation
Pyretogens or pyrogenics	pyrétogènes, pyrogènes; fiebertreibende or fiebererregende M.	inducing fever
Refrigerants	réfrigérants; Refrigerantien, abkühlende M.	relieving fever, thirst
Remedies	remèdes; Heilm.	curing or preventing disease
Resolvents	résolutifs, résolvants; Resolventien, Lösungsm.	promoting resolution or dissipation of pathological growth
Restoratives	reconstituants; Wiederherstellungsm.	promoting return to health or consciousness
Revulsives or revulsants	révulsifs; ableitende M.	causing revulsion, or drawing of blood from one part of the body to another
Roborants	roboratifs, fortifiants; roborierende M.	conferring strength
Rubefacients	rubéfiants; hautrötende M.	reddening the skin
Salivants	salivants; speicheltreibende M., Salivantia	provoking saliva
Sedatives	sédatifs; Beruhigungsm., Nervenm.	allaying excitement/activity
Sialagogues	sialagogues; Sialagoga	promoting salivary flow

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Somnifacients		*See* "Soporifics"
Soporifics	somnifères; Schlafm.	inducing profound sleep
Specifics	spécifiques, Specifica	medicines that have distinct curative influence on a particular disease
Spermatopoietics	spermatopoïétiques; samenbildende M.	promoting semen secretion
Spirocheticides	spirochéticides; spirochäticide M.	destroying spirochetes
Sternutatories		*See* "Errhines"
Stimulants	stimulants, excitants; Stimulantien, Reizm.	causing stimulation
Stomachics	stomachiques; Magenm.	promoting stomach activity
Styptics	styptiques; Styptica, blutstillende M.	arresting hemorrhage by astringent action
Sudorifics	sudorifiques; Schwitzm., schweisstreibende M.	promoting sweating
Surrogates	succédanés; Ersatzm., Surrogate	substances used as substitutes
Sympathicolytics	sympathicolytiques; sympathikolytische M.	inhibiting autonomic nerve impulse transmission
Sympath(ic)omimetics	sympathicomimétiques; sympathikomimetische M.	producing effect resembling that caused by stimulation of sympathetic nervous system
Teniacides	ténicides; Bandwurmm.	destroying tapeworms
Teniafuges	ténifuges; Bandwurmm.	expelling tapeworms
Tonics	toniques; Tonica, tonisierende M.	restoring normal tone
Topical agents	topiques; Topica	medicines for local external application
Vaccines	vaccins; Vakzine, Impfstoffe	substances used for preventive inoculation
Vasoconstrictors	vasoconstricteurs; Vasokonstriktoren, gefässverengernde M.	causing blood vessel constriction
Vasodilators	vasodilatateurs; Vasodilatatoren, gefässerweiternde M.	causing blood vessel dilation
Vehicles	véhicules; Vehikel	excipients
Vermicides	vermicides; Vermicida	destroying intestinal animal parasites
Vermifuges	vermifuges; Wurmm., Vermifuga	expelling worms or intestinal animal parasites
Vesicants	vesicants; Vesicatoria, Vesicantia, blasenziehende M.	causing blisters
Viru(li)cides	virulicides; virustötende M.	destroying viruses
Vomitants, -ives		*See* "Emetics"
Vulneraries	vulnéraires; wundenheilende M.	healing wounds

Table III. Latin and Greek Prefixes, Combining Forms, and Suffixes Used in French and German Biochemical and Medical Terms[a]

1. General Prefixes

a-	negative	ap-	*See* ad-
ab-	away from, down	ap(o)-	away from, detached, off
ac-	*See* ad-	as-	*See* ad-
ad-	to, at, toward	at-	*See* ad-
af-	*See* ad-	bi-	two, twice
ag-	*See* ad-	cat(a)-	down, negative
amphi-	both, doubly	circum-	around
an-	*See* a-	co-	*See* con-
an(a)-	positive, up, through	col-	*See* con-
ant(i)-	against, counter	com-	*See* con-
ante-	before	con-	with, together

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contra-	against, counter
cor-	*See* con-
de-	down from
di-	two
di-	*See* dia-
dia-	through, apart
di(s)-	apart, away from
e-	out from
ec-	out of
ef-	*See* ex-
em-	*See* en-
en-	in, on
endo-	inside
ep(i)-	above, over, upon, after, in addition
eso-	inside
ex-	out of
exo-	outside
extra-	outside of, beyond
hemi-	half
heno-	one
hept-	seven
hex-	six
il-	in, on, negative
im-	in, on, negative
in-	in, on, negative
infra	beneath
inter-	among
intra-	inside
ir-	in, on, negative
medi-	middle
meso-	middle
mon(o)-	single, only, sole
non-	nine
ob-, oc-	against, toward
para-	through, beside, near, also denoting abnormality
pent(a)-	five
per-	through
peri-	around, near
poly-	much, many
post-	after, behind in time or place
pre-	before in time or place
pro-	before in time or place
re-	back, again
retro-	backwards
semi-	half
sept-	seven
sub-, suf-, sup-	under, below
super-	above, beyond, extreme
syn-, sy-, syl-, sym-	with, together
tele-	at a distance, far off
tetr-	four
tri-	three
un(i)-	one, single

II. Specific Prefixes and Combining Forms[b]

acou-	G	hear	acoumétrie, Akustik
acr-	G	extremity, peak	acrocéphalie, Akrozyanose
actin-	G	ray, radius	actinomycète, Aktinotherapie
aden-	G	gland	adénopathie, Adenom
adip-	L	fat	adipeux, Adiposurie
alb-	L	white	albuginé, Albumosen
all-	G	other, different	allélomorphe, Allergen
amyl-	G	starch	amylacé, Amylose
andr-	G	man	androgène, Andrologie
angi-	G	vessel	angiologie, Angiom
ankyl-	G	crooked, looped	ankyloglosse, Ankylostomiasis
arachn-	G	spider	arachnodactylie, Arachnitis
arch-	G	beginning, origin	archencéphale, archenteral
arthr-	G	joint	arthrose, Arthropathie
articul-	L	joint	articulation, artikulär
ästhe-		*See* esthe-	Ästhesiometer
aur-	L	ear	auriste, Auripunktur
auto-	G	self	autoséroréaction, Autotransfusion
aux-	G	increase	auxoflore, Auxokardie
ba-	G	go, walk, stand	dysbasie, Abasie
balneo-	L	bath	balnéologie, Balneotherapie
bary-	G	heavy, difficult	barytron, Baryphonie
bio-	G	life	biotype, Biopsie
blast-	G	bud, child, a growing thing in its early stages	blastoderme, Blastophthorie
blephar-	G	eyelid	blépharospasme, Blepharostat
brachi-	G	arm	brachiotomie, Brachialneuralgie
brachy-	G	short	brachycéphale, Brachyphalangie
brady-	G	slow	bradycardie, Bradykinesie
brom-	G	stench	bromoménorrhée, Bromidrosis
bronch(o)-	G	windpipe	bronchorrhée, Bronchektase
cac-	G	bad, abnormal	cacophonie, Kachexie
calc-	L	stone	calculeux, kalkig

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calc-	L	heel	calcanéoplantaire, Calcaneuswinkel
calor-	L	heat	calorimètre, kalorisch
canc(r)-	L	crab, cancer	cancérigène, kankroid
capit-	L	head	capiteux, Decapitator
caps-	L	container	encapsulé, Kapsel
carcin-	G	crab, cancer	carcinomateux, Karzinose
cardi(o)-	G	heart	cardiotonique, kardiovaskulär
cary-	G	kernel, nucleus	caryocinétique, Caryotheca
cat-	G	down, negative	catélectrotonus, Kathode
cata-		*See* cat-	catabolisme, katatonisch
caud-	L	tail	caudocéphalique, kaudal
cav-	L	hollow	cavicole, kavernös
c(a)ec-	L	blind	cécité, Caecopexie
cel-	G	hollow	céloscope, Coelophlebitis
cell-	L	room, cell	cellulite, zellenförmig
c(o)en-	G	common	cénesthésie, Coenobia
cephal-	G	head	céphalalgie, Kephalhämatom
cer-	L or G	wax	cérome, Zerate
chancr-		*See* cancr-	chancroïde, for Gm. cf. "schankr–"
cheil-	G	lip	chéilite, Cheiloplastik
cheiro-	G	hand	cheiro-pompholyx, Cheirospasmus
chir(o)-		*See* cheiro-	chiragre, Chiromegalie
chlor-	G	green	chlorose, Chlorom
chol-	G	bile	cholérèse, Cholangiographie
chondr-	G	cartilage	chondrite, Chondriomiten
chro-	G	color	chromatopsie, Chromosom
chron-	G	time	chronique, Chronaxie
cili-	L	eyelid, eyelash	ciliogénèse; Ciliotomie, Ziliarnerv
cine-	G	move	cinésithérapie, Dyskinesie
-cis-	L	cut, kill	abscision, Exzision
clino-	G	bend, incline, lie down	clinocéphalie, klinostatisch
coel(i)o-	G	belly	coelomique, Cöliotomie
colp-	G	vagina	colpite, Kolpokleisis
copr-	G	dung	coproculture, koprophag
cor-	G	image, pupil	corémorphose, Koretomie
cortic-	L	bark, rind	cortico-surrénale, kortikospinal
cost-	L	rib	costo-vertébral, kostoklavikular
creat-	G	meat, flesh	créatotoxisme, Kreatoxikon
crin-	G	distinguish, separate off	endrocrinose, endokrin
crur-	L	shin, leg	crural, Kruralindex
cry-	G	cold	cryoscopie, Krymotherapie
crypt-	G	hide, conceal	cryptorchidie, Krypten
cune-	L	wedge	cunéiforme, Cuneohysterektomie
cut-	L	skin	cutisation, subkutan
cyan-	G	blue	cyanophil, zyanotisch
cyst-	G	bladder	cystite, Zystoskop
cyt-	G	cell	cytotoxine, Zytolysin
dacry-	G	tear	dacryocystite, Dakryorrhoe
dactyl-	G	finger, toe	dactylite, Daktylogramm
dendr-	G	tree	dendritique, Dendrit
dent-	L	tooth	dentifrice, Dentikel
derm(at)-	G	skin	dermatite, Dermatologe
dermo-		*See* derm-	dermopathie, Dermographie
desm-	G	band, ligament	desmopathie, Desmobakterien
dextr-	L	right	dextrogyre, Dextrokardie
didym-	G	twin, testis	didyme, Epididymis
digit-	L	finger, toe	digitation, Digitalis
diplo-	G	double	diplocoque, Diplobazillus
dors-	L	back	dorsoventral, dorsal
dur-	L	hard	durillon, Induration
dynam-	G	force, power	dynamomètre, dynamisch
dys-	G	bad, difficult, faulty, defective, painful	dyscrasie, Dysmenorrhoe
ect-	G	out, outside	ectoderme, ektopisch
enter(o)-	G	intestine	entérocèle, Enterokolitis
erg-	G	work, deed	ergographe, Ergometer

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erythr-	G	red	érythropsie, Erythrozytose
esthe-	G	perceive, feel	esthésodique, for Gm. cf. "ästh-"
eu-	G	good, normal	eupeptique, Eutokie
fasci-	L	band	fasciculé, Faszie
febr-	L	fever	fébrifuge, febril
flav-	L	yellow	flavisme, Flavoprotein
front-	L	forehead, front	front, nasofrontal
fund-, fus-	L	pour	infusion, Perfusion
galact-	G	milk	galactagogues, Galaktosurie
gam-	G	marriage, reproductive union	gamètes, agamisch
gastr-	G	stomach	gastrogène, Gastroileitis
gelat-	L	freeze, congeal	gélatinisation, gelatinös
gem-	L	twin, double	gémellaire, gemmipar
gen-	G	produce, originate	génétique, Genodermatose
genio-	G	chin	génioplastie, Geniospasmus
gest-	L	bear, carry	gestation, Gestose
gloss-	G	tongue	glossite, Glossektomie
glott-	G	tongue, language	épiglotte, glottisch
gluc-	G	sweet	glucose, Glukoproteid
glyc(y)-		*See* gluc-	glycogénie, Glykogeusie
gnath-	G	jaw	gnathoschisis, Brachygnathie
gno-	G	know, discern	barognosie, Diagnose
grad-	L	walk	retrograde, digitigrad
grav-	L	heavy	gravide, Primigravida
gyn-	G	woman, wife	gynandrie, Gynäkologe
häm(at)-		*See* hem-	Hämolyse, hämatopoietisch
haplo-	G	simple, single	haploïde, Haplobakterien
hapt-	G	touch	haptophobie, Haptotaxis
helc-	G	sore, ulcer	helcologie, Helkoplastik
hem(at)-	G	blood	hémangiectasie, hématogène
hemo-		*See* hem-	hémothérapie, for Gm. cf. "häm-"
hepat-	G	liver	hépatogène, hepatophlebitis
hered-	L	heir	hérédocellulaire, Herodotaxie
hetero-	G	different, opposite	hétérotropie, Heterovakzin
hist-	G	web, tissue	histologie, Histophysiologie
hom(o)-	G	common, same	homogène, homolateral
horm-	G	impetus, impulse	hormonal, Hormon
hydat-	G	water	hydatide, Hydatidenschwirren
hydr-		*See* hydat-	hydriatrie, Hydrarthrose
hyper-	G	above, excess, extreme, abnormality in amount, size, quality, etc.	hyperpnée, Hypertonie
hypno-	G	sleep	hypnolepsie, Hypnose
hypo-	G	under, below, diminution as to degree, amount, quality, etc.	hypohydrose, Hypocalcämie
hyster-	G	womb, uterus	hystérocèle, Hysteriographie
iatr-	G	physician	iatrophysicien, Iatrochemiker
idi-	G	own	idiotrope, Idioplasma
ile(o)-	L	lower abdomen, intestines, ileum	iléite, Ileostomie
ili(o)-		*See* ileo-	iliothoracopage, Iliadelphus
insul-	L	island	insuline, Insulom
irid(o)-	G	rainbow, colored circle, ref. to iris	iridocèle, Iridodialyse
iso-	G	equal, like	isochrome, Isocytolysin
ischi-	G	hip, haunch	ischiocèle, Ischialgie
jact-	L	throw	jactation, Jactatio
ject-		*See* jact-	injection, Dejektion
jejun-	L	empty, ref. to jejunum	jéjunite, Jejunostomie
jo(u)nct-	L	yoke, join	conjonctivite, Conjunctiva

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kary-		*See* cary-	karyogamie, Karyolyse
kata-		*See* cat-	Kataphorese
kerat-	G	horn	kératite, Keratom
kine-		*See* cine-	kinesthésie, Kinästhesie
labi-	L	lip	labiographe, Labiologie
lact-	L	milk	galactocèle, Lactobiose
lal-	G	talk, speech, babble	lalophobie, Laloplegie
lapar-	G	flank	laparoscopie, Laparotomie
laryng-	G	windpipe	laryngologiste, Laryngozentese
later-	L	side	latéroflexion, Laterognathie
lepto-	G	thin, narrow, weak	leptoproscopie, leptosom
leuc-	G	white	leucémique, Leukocyt
lien(o)-	L	spleen	liénographie, Lienomalcie
lig-	L	tie, bind	ligamenteux, Ligatur
lingu-	L	tongue	linguocclusion, sublingual
lip-	G	fat	lipoblaste, Lipacidämie
lith(o)-	G	stone	lithectomie, Hepatolith
log-	G	speak, word	logasthénie, Logoklonie
l(o)umb-	L	loin	lombaire, sacrolumbal
lute-	L	yellow	lutéine, Luteohormon
lys-	G	loose, dissolve	lysines, Lyse
lymph-	L	water, ref. to lymph glands	lymphocytose, Lymphangitis
macr(o)-	G	long, large (often abnormally so)	macrocyte, Makrogamet
mal-	L	bad, abnormal	malformation, Malaria
malac-	G	soft	malacoplasie, Malakoplakie
mamm-	L	breast	mamillaire, mammotrop
mast-	G	breast	mastopathie, Mastoptose
mega-	G	great, large	mégastrie, Megalomanie
melan(o)-	G	black	mélanosarcome, Melanodermie
men-	G	month	ménopause, Menarche
mening-	G	membrane	méningite, meningovasculär
ment-	L	mind	mentalité, Mentalsuggestion
meta-	G	denoting transition, change	métastase, Metabolismus
metr-	G	womb	métrite, Metrektomie
micro-	G	small	micro-organisme, Mikrospore
mimet-	G	imitation	sympathicomimétique, parasympathikomimetisch
mne-	G	remember	dysmnésie, Anamnese
morph(o)-	G	form, shape	morphogénèse, morphotisch
mot-	L	move	motricité, Motorik
myel(o)-	G	marrow, ref. to brain or spinal cord	myélopoïèse, Myelocytose
myo-	G	muscle	myoclonique, Myokard
myx-	G	mucus	myxome, Myxorrhoe
narc(o)-	G	stupor	narcolepsie, Narkotismus
necro-	G	dead body	nécropsie, Nekrose
neo-	G	new, young, recent	néoplasme, Neophilismus
nephr-	G	kidney	néphralgie, nephritisch
neu(v)r-	G	nerve	névralgique, Neurasthenie
nod-	L	knot	nodosité, nodös
nos-	G	disease	nosophobie, nosotrop
oc(k)ul-	L	eye	oculocardique, okulär
oede-	G	swell	oedème, ödematös
odont(o)-	G	tooth	odontogène, Odontoklast
ole-	L	oil	oléothorax, Oleinat
olig(o)-	G	few or lack of	oligodynamique, Oligophrenie
omphal-	G	navel	omphalite, Omphalektomie
onc(o)-	G	tumor	oncologie, onkolytisch
onych(o)-	G	claw, nail	onychoïde, Onychophagist
oo-	G	egg	oophorite, Oospore
opht(h)alm-	G	eye	ophtalmoscope, Ophthalmoplastik

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or-	L mouth	peroral, oral
orchi-	G testicle	orchiocèle, Orchiodynie
ortho-	G straight, right, normal	orthopédie, Orthodontie
oss-	L bone	ossification, Ossikulektomie
ost(eo)-	G bone	ostéo-arthrite, Osteokarzinom
ot(o)-	G ear	otite, Otoblennorrhoe
ov-	L egg	ovalbumine, Ovariocentese
oxy-	G sharp, quick or sour	oxyopie, Oxytocicum
pachy-	G thicken	pachychéilie, Pachyblepharon
pan-	G all, every, universal	panartérite, Panplegie
par(t)-	L bear, give birth	parturiente, Nullipara
path(o)-	G that which one undergoes, sickness	pathogénèse, pathologisch
pe(ä)d-	G child	pédiatre, Pädatrophie
pell-	L skin, hide	pellicule, pellagrös
peps(t)-	G digest	pepsinogène, Dyspepsie
phac(o)-	G lentil, lens	phacosclérose, Phakoskop
phag-	G eat	phagocyte, phagedänisch
phak-	*See* phac-	phakitis, Phakolyse
phil-	G like, have affinity for	philonéisme, Basophilie
phleb-	G vein	phléborragie, Phlebektasie
phleg-	G heat, inflammation	phlegmasie, Phlegmone
phos-	G light	phosphène, Phosphor
phot-	*See* phos-	photobiologie, Photobakterie
pht(h)i-	G decay, waste away	phtisique, Phthisiotherapie
phyl(o)-	G tribe, kind	phylogénique, Phylogenie
phylac(x)-	G guard	anaphylactique, Phylaxis
phys(o)-	G air	physométrie, Physocephalus
pil-	L hair	épilatoire, pilomotorisch
plas-	G mold, shape	néoplasme, Plastizität
platy-	G broad, flat	platypodie, Platykranie
pleur-	G rib, side	pleurosome, Pleurothotonus
pne-	G breathing	dyspnée, Pneograph
pneum(at)-	G breath, air	pneumatoscope, Pneumatometrie
pneumo(n)-	G lung	pneumobacille, Pneumonozentese
pod-	G foot	podalgie, Podobromidrose
p(o)unct-	L prick, pierce	ponction, Renipunktur
proct-	G anus	proctectomie, Proktocele
prosopo-	G face	prosopoplégie, Prosopospasmus
pseud-	G false, spurious	pseudomyxome, Pseudomyopie
puber-	L adult	puberté, Pubertät
pur-	L pus	purulent, Suppuration
pyel(o)-	G trough, basin, ref. to pelvis	pyélectase, Pyelographie
pyl-	G door, orifice	pyléphlébite, Pylorus
pyo-	G pus	pyogène, Pyorrhoe
pyr(o)-	G fire, heat	pyrogène, Pyrosis
rachi-	G spine	rachicentèse, Rachianästhesie
radi-	L ray	radiologie, radioaktiv
ren-	L kidney	réniforme, Renographie
ret-	L net	réticulome, Reticulocyt
rhin(o)-	G nose	rhinoplastie, Rhinophyma
rub(r)-	L red	rubéole, rubrospinal
sarc-	G flesh	sarcolyse, Sarkoblast
schankr-	*See* chancr-	Schankröswerden
schis(z)-	G split	schistocyte, Schizogonie
scler-	G hard	sclérite, Sklerodermie
sens-	L perceive, feel	sensoriel, Sensomotilität
sep-	G rot, decay, putrid	septicémie, Septokopyämie
sial-	G saliva	sialome, Sialodochitis
sin-	L cavity	sinus, Sinuspunktion
sit-	G food	sitiomanie, Sitiophobie
somat-	G body	somatique, somatotrop
somn-	L sleep	somnifère, Somnolenz
sphen-	G wedge	sphénocéphalien, sphenoid

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sphygm-	G	pulse, pulsation	sphygmocardiogramme, Sphygmotonometer
spirat-	L	breathe	respiratoire, Inspiration
splen-	G	spleen	mégalosplénie, Splenopexie
spor-	G	seed	sporulation, Sporozoose
squam-	L	scale	desquamation, squamös
stear-	G	fat	stéarrhée, Stearin
steat-		*See* stear-	stéatopygie, Steatitis
sten-	G	narrow, compressed	sténothorax, Stenostomie
ster-	G	solid	astéréognosie, stereognostisch
sterc-	L	dung	stercorémie, Stercobilin
sthen-	G	strength	asthénie, sthenisch
strep(h)-	G	twist	streptobacille, Strephopodie
tachy-	G	speed, swift	tachycardie, Tachypnoe
tel-	G	end	télencéphale, Teleangitis
ten(o)-	G	ref. to a tendon	ténodèse, Tenontodynie
thel-	G	teat, nipple	thélite, Thelorrhagie
therm-	G	heat	thermochimie, Thermästhesie
thi-	G	sulfur	thiochrome, Thiourea
thorac-	G	chest	thoracopage, Thorakoschisis
thromb-	G	lump, clot	thrombopathie, Thrombose
thym-	G	spirit	thymogène, Hyperthymie
thyr-	G	shield, rel. to thyroid	thyréopexie, Thyreoiditis
toc-	G	childbirth	oxytocique, Dystokie
tox-	G	poison	toxicose, Toxikodermie
trache-	G	windpipe	trachéophonie, Tracheopyosis
trachel-	G	neck	trachelhématome, Trachelismus
traumat-	G	wound	traumatopnée, Traumatologie
trich-	G	hair	hypertrichose, Trichitis
trop-	G	turn, react	tropomètre, Tropismus
troph-	G	nurture	trophopathie, trophisch
typhl-	G	blind	typhlolexie, Typhlologie
ulo-	G	rel. to the gums	ulotomie, Ulorrhagie
vas-	L	vessel	vasectomie, Vasalgie
vesic-	L	bladder	vésiculite, prostaticovesical
vit-	L	life	vitalisme, Vitalität
xanth-	G	yellow, blond	xanthopsie, Xanthodermie
zo(o)-	G	life, animal	zoogénique, Zoonose
zyg-	G	yoke, union	zygomatique, Zygapophyse
zym-	G	ferment	enzyme, zymogen

III. Specific Suffixes[c]

-agogue(-gum)	G	leading, inducing	cholagogue, Emmenagogum
-agra(-e)	G	attack, seizure	pellagre, Podagra
-algie	G	pain	thélalgie, Rheumatalgie
-aphie	G	touch	oxyaphie, Amblyaphie
-cele	G	tumor, hernia, protrusion	myélocèle, Kolpocele
-centese	G	puncture	paracentèse, Enterozentese
-cid(e)	L	cut, kill	bactéricide, fungicid
-clasie(-s)	G	breaking down	cytoclasie, Mucoclasis
-clast	G	instrument for breaking	crânioclaste, Myeloclast
-ectomie	G	cut out, excision	hystérectomie, Appendektomie
-e(ä)mie	G	blood, denotes a condition of the blood or an ingredient in blood	anémie, Toxämie
-dynie	G	pain	protodynie, Pododynie
-eurynter	G	dilate	métreurynter, Hystereurynter

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-ferent	L	bear, carry	efférent, afferent
-fuge(-a)	L	flee, expel	vermifuge, Febrifuga
-genese	G	production	lactogénèse, Gamogenese
-gramm(e)	G	write, record	encéphalogramme, Elektrokardiogramm
-graph(i)e	G	write, record	sphygmographe, Splenographie
-ite, -itis	G	denoting inflammation	thyroïdite, Myelitis
-logie	G	discourse, treatise upon or science of	sitiologie, Somatologie
-lyse	G	loosening, dissolving, separation into constituent parts	autolyse, Glykolyse
-malacie	G	soft, abnormal softness	myomalacie, Encephalomalacie
-manie	G	mental aberration	mythomanie, Trichomanie
-megalie	G	great, large (abnormally so)	splénomégalie, Gastromegalie
-mer(e)	G	part	monomère, polymer
-metre(-ter)	G	measure, instrument for measuring	hématimètre, Myotonometer
-mycet(e)	G	fungus	schizomycète, Blastomycet
-od(e)	G	form	plasmode, Nematod
-odynie	G	pain, distress	ostéodynie, Glossodynie
-oid(e)	G	form, similar in shape, etc.	fongoïde, typhoid
-om(e)	G	tumor	sarcome, Myxadenom
-op(s)ie	G	see, pert. to eye or vision	myopie, Xanthopsie
-page(-gus)	G	fix, make fast	thoracopage, Sternopagus
-pathie	G	a condition of disease, also a method of cure	hépatopathie, Kardiopathie
-penie	G	lack, deficiency	érythropénie, Thrombopenie
-pepsie	G	digest	dyspepsie, Autopepsie
-pexie	G	fixation	orchidopexie, Typhlopexie
-phag(i)e	G	eat	aérophagie, Bakteriophage
-pher(i)e	G	bear, support	périphère, Peripherie
-phil(e)	G	affinity for	neutrophile, eosinophil
-phobie	G	dread, morbid or exaggerated fear	ergophobie, Gynäkophobie
-phonie	G	sound	bronchophonie, Aphonie
-phren(ie)	G	mind	hébéphrénie, schizophren
-phyll(e)	G	leaf	xanthophylle, Chlorophyll
-phyt(e)	G	beget, produce	zygophyte, Anaerophyt
-plastie(-ik)	G	to form	proctoplastie, Rhinoplastik
-plegie	G	stroke, paralysis	hémiplégie, Paraplegie
-plexie		*See* -plegie	apoplexie, Kataplexie
-po(i)ese	G	make, produce	chylopoïèse, Hämatopoese
-pore(-us)	G	opening, passage	myelopore, Blastoporus
-rr(h)ag(ie)	G	break, burst, hemorrhage or excessive discharge	hémorragie, Metrorrhagie
-rr(h)aph(ie)	G	suture	myorraphie, Orchidorrhaphie
-rrhexie, -xis	G	break, burst	amylorrhexie, Angiorrhexis
-rrhée(-öe)	G	flow, excessive discharge or excretion	diarrhée, Galaktorrhoe
-scop(ie)	G	look at, observe	thoracoscope, Sphygmoskopie
-sclerose	G	hardening	cardiosclérose, Arteriosklerose
-som(e)	G	body	chromosome, Autosom
-stase	G	make stand, stop, inhibit	hémostase, Cytostase
-stomie	G	surgical operation in which an artificial opening or passage is formed	caecostomie, Typhlostomie

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-taxie(-s)	G	arrangement	ataxie, Epistaxis
-tomie	G	cut, an incision	ténotomie, Tracheotomie
-trop(e)		*See* Prefixes	
-troph(e)		*See* Prefixes	
-ulus, -ula, -ulum, -ola, -ion, -ellus, -illus, -leus		diminutives	
-urie	G	urine, abnormalities of the urine or of urination	albuminurie, Hämaturie

[a] In view of the fact that there is as yet no agreement on the use of the German consonants *c*, *k*, and *z* in the spelling of many foreign terms of Greek and Latin origin, many prefixes, combining forms, and suffixes normally written with *c* are frequently also written with *k* or *z* in German. These alternative spellings have not been separately listed.

[b] Some of the forms listed here occasionally appear as suffixes as well.

[c] Some of the forms listed here occasionally appear as prefixes and combining forms as well.

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Literature of the Chemical Periphery—Embalming

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The literature of embalming has been virtually unknown to and hence ignored and unexplored by the scientific public. With the intent to make accessible and extend contiguously that frontier of knowledge, an introduction to the literature of embalming is presented, together with a short historical sketch. Comprehensive monographs, specialty items, and books published since 1930 are given particular attention. Tables show embalming schools currently operating, trade associations in the field, and some fluid companies maintaining research laboratories. A check list of embalming periodicals is provided, with a few indications of library holdings. A chronological bibliography of embalming literature includes subsections on encyclopedia articles and Egyptology.

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There is a saying that even a shy man can be eloquent in his own field. However, the author is not an embalmer—nor even one of Dostoievsky's "These Living Dead" or Gogol's "Dead Souls." One can scarcely mention embalming without eliciting a smile from one's hearers—whether this stems from embarrassment, true humor, or a grim determination to be Pollyanna in the face of death. Because of this attitude, it seems well to tell at the outset a few lighter incidents within the history of embalming before plunging into the pall of its literature. Among predecessor chemists interested in this art may be mentioned Kolbe of the classical syntheses, Jerome Alexander, and Harry Deuell.

"What a dry skeleton," says Peacock *(40)*, "is the history of Rome, told by one who believes nothing that the Romans believed." The Egyptians, Assyrians, and Hindus at one stage in their history preserved their dead with beeswax and then with honey, while the ancient Hebrews used aloes and spices for the same purpose.

Alexander the Great, for instance, was embalmed with honey *(6)*. One school of thought has it that this was just to keep things sweet until he could be brought home, as was the case with Agesipolis, the Spartan leader. In any event, it was a sticky proposition. Embalming or mummification to preserve the body indefinitely has been applied to kings, religious leaders, and great public figures in all ages. King Canute, the pioneer in wave mechanics, was embalmed (and lasted a good 740 years, too), as were successive British rulers, such as William the Conqueror, and his Queen Matilda, Edward I, Henry I, Charles I, to mention a few firsts. Members of other ruling houses have been treated similarly. This included the Russian czars, who were interred in the walls of the Kremlin. A former employee of the Soviet Central Secretariat said that when the Bolsheviks first came into control in 1918, a group of them rushed into the Kremlin and opened several royal tombs, with the idea of making a mocking show. The third sepulcher unsealed was that of Ivan Groznyi (Ivan the Terrible or Ivan IV). He looked so fierce still, in his excellent state of preservation, that he unnerved the group, and they silently closed the lids, restored the bodies to their resting places, and slunk away. Whether any change was made later is not known. One is bound to be curious about the wonderful job of embalming done on Lenin. It was fairly common knowledge at the time of Lenin's death that his body was so badly ravaged by disease that it had to be disposed of quickly, and a dead double found to serve for the populace. Nevertheless, the em-

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

balming job done on the stand-in (or lie-in, if you prefer) is reputedly a very fine one *(2)*.

Rumor has also asserted that a fresh stand-in was substituted about 1934. Whitehead has remarked "If men cannot live on bread alone, still less can they do so on disinfectants *(54)*."

Numerous popes, cardinals, and church prelates have been accorded lasting embalmment. Cardinal Richelieu *(17)* is an instance. There is a whole order of Capuchin monks in Sicily, the dead members of which have been preserved by desiccation in the grottoes of a cave near Palermo. Among the U. S. Presidents, the case of Abraham Lincoln is most interesting in that eye-witness accounts *(8)* of the opening of his coffin in 1901 at Springfield, Ill., differ as to the quality of the state of preservation obtaining. Credence goes to the man who reported it as greenish in color and exhibiting skin slip.

Everyone is, no doubt, also familiar with Hunter's account *(25)* of how the Egyptian railroad ran the first 10 years of its existence, using mummies as fuel to generate its steam. Mark Twain in "Innocents Abroad" quotes the engineer as saying to the fireman, "These common folk don't burn worth a damn. Send me a King!" Hunter tells, too, of the importation of mummies into the United States purely to supply linen rags to make paper. This was before the advent of chemical wood pulp. Here McCurdy quotes Donnelly *(16)*: "Quantities of these weird yet interesting corpses (Egyptian mummies) have been appropriated for fuel by the Arabs, while whole shiploads have been converted into manure by the avaricious Englishmen for the growing of turnips." In medieval times, and carried well down through the 19th century, mummy dust was considered a potent drug for internal consumption for whatever ailed you.

Whereas the Egyptian and Abyssinians went in for embalming of two different types, the people of Uganda, who are communicably adjacent to the south, preserve only the lower jaw bone of a king, and his umbilical stump, wrapped in decorated bark cloth, believing that the ghost of a dead man adheres to the lower jaw bone, and the ghost of his double to his navel string. Each king, however, must have a separate tomb, because otherwise there would be quarrels of precedence and protocol among the ghosts *(44)*. In this connection passing reference may be made to a discussion by Cabanes *(7)*, on the relation of the umbilicus to intelligence.

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Introduction to Literature on Embalming

This paper with its bibliography provides an introduction to the literature of embalming, and related funeral matters. It does not purport to be a complete record—i.e., exhaustive of all such literature—but rather to offer a convenient point of debarkation to anyone interested in studying a particular phase of the art, or science, or its history (which parallels that of the human race). It does not describe the process or processes of embalming, or the nature of the chemicals so employed, except incidentally. Reference to taxidermic art has been kept to a minimum.

The first comprehensive bibliography of embalming was that of McCurdy *(31)* published in 1896, which comprises the second 40-page part of his doctoral dissertation. John Townsend had published a partial catalog of books and journal references on this subject in 1887, and there was a compilation in the Surgeon General's first "Catalog," too. The second comprehensive bibliography on embalming is that of E. H. McClelland *(30)*, a mimeographed report (edition of 100 copies only) issued to the National Association of Colleges of Mortuary Science, Inc., May 31, 1949, which, in turn, distributed copies of the report to its member schools. It has become a scarce item.

The McClelland bibliography includes classified lists of books in certain related funerary fields not deemed pertinent to this paper, such as:

Accounting and other business methods (for funeral directors)
Apparent death and premature burial
Brasses, memorial
Burial
Catacombs
Cemeteries
Consolation
Cremation
Death

Death masks
Epitaphs and inscriptions
Exhumation and reinterment
Funeral rites, ceremonies, and customs
Funeral sermons and addresses
Funeral services and obsequies
Identification of the dead
Megaliths and cromlechs
Monuments, sepulchral
Monuments and cemeteries, military
Mortuary laws
Mound burial
Mummies
Obituaries
Sarcophagi
Tombs
Urn burial
Miscellaneous
  Casket manufacture
  Flower arrangement
  Formaldehyde
  Incense, etc.

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Historical Discussion

Embalming, as defined by Carruth *(9)*, is the art and science of disinfecting, preserving, and beautifying the dead human body for funeral purposes. A distinction in meaning has been made between embalmment and embalming. Embalmment refers to old-style preservation of human remains involving physical removal of the internal organs of the body, soaking and packing the cavities with chemicals, followed by natural or induced dehydration. Embalming refers only to the modern method of preservation through arterial injection of chemicals. The custom of embalming is said to have originated on the legendary island of Atlantis among its sun-worshipping people, and to have spread from there to the Guanches in the Canary Islands, to Egypt, Mesopotamia, and other inhabited parts of the world. It has been practiced in Peru, Mexico, among North American Indians from Florida to Oregon, and elsewhere. Therefore, it seems likely that embalming may have developed independently and spontaneously in separate parts of the world, and usually where climatic conditions helped to abet the early practitioners. All peoples honor their dead. The idea of preservation of the body after death probably arose in connection with religious beliefs. Certainly, it did among the Egyptians, who had strict religious rites and believed in the immortality of the soul. The priestcraft officiated. Gradually, a separation of priestly and surgico-physician's function occurred.

The practice of embalming became the professional prerogative of physicians, particularly in Egypt, and it may have been the first medical specialty with separate training requirements and standards. Hambly *(24)* has reported what may well be another possible first for the Egyptians. He describes examples of humor in animal drawings made about 1100 B.C. for relaxation by Egyptian artists employed in a cemetery at Thebes to decorate tombs. It is still the legal prerogative of physicians in the various Latin American countries. A solitary exception exists at present in Monterrey, Mexico, where a graduate of an American embalming school has been granted the right to practice embalming by the local medical society. Changes in the laws will undoubtedly occur as conditions warrant.

Ancient embalming or mummification was essentially desiccation. Thus, the Egyptians didn't have to do too good a job, on account of their climate. Those Egyptian mummies, which have been transported to the British Museum in London, are deteriorating faster than those stored anywhere else in the world, owing to the damp English climate. It was not until after Harvey's discovery of the circulation of the blood about 1600 that arterial injection was tried. Frederick Ruysch is conjectured to have first practiced arterial preservation in embalming specimens for the medical school in Amsterdam between 1665 and 1717, but a precise date cannot be deduced. Ruysch was noted for his method of injecting blood vessels, and he also demonstrated the lymphatic valves. Ruysch's collection of mummies was sufficiently famous in his day to attract two visits from Czar Peter the Great, and eventually that monarch purchased the collection and transported it to Russia.

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Baas *(4)* says, "Ruysch advanced anatomy by the formation of anatomical collections, one of which was brought into Russia by Peter the Great at an expense of about $75,000. The Russian transporters of the collection, however, drank the alcohol in which the collections were preserved and a portion of it was ruined." The collection also inspired the Italian philosopher and poet, Leopardi, to write the "Dialogue between Frederick Ruysch and His Mummies" *(29)*, which opens with one of his finest lyrics, "The Chorus of the Dead in the Laboratory."

The Scotch surgeon William Hunter is usually recognized as the first to embalm arterially. His surgeon brother, John Hunter, also carried out extensive experiments of this nature. Several specimens of their handiwork were on exhibition in the Hunterian Museum of the Royal College of Surgeons in London, until a Nazi bomb destroyed the wing in 1941. One of the most famous of these specimens was that of Mrs. Van Butchell. Martin Van Butchell was a pupil and friend of John Hunter. He is sometimes alluded to as a quack, but considering the medical education of that time he had about as good a one as the next fellow, and probably his ethics matched, too. Now, Van Butchell was married to a beautiful lady who was his delight. Sad to relate, she died at the early age of 36 "of empyema of the left lung." Van Butchell turned to his mentor, John Hunter, for assistance, and a thorough embalming job was performed upon her, using Venice turpentine, vermillion, etc. Van Butchell himself participated in the operation as well as the anatomist, William Cruikshank. Van Butchell then brought home his embalmed wife, dressed her in her finest frock, and sat her in the parlor to keep him company of an evening. The news leaked out and the force of curiosity being what it is, Van Butchell had to arrange a visiting hour schedule for the neighbors and members of the vulgar crowd interested in this scientific curiosity. The notice he issued, still preserved, reads:

> Van Butchell (not willing to be unpleasantly circumstanced, and wishing to convince some good minds they have been misinformed) acquaints the Curious, no stranger can see his embalmed wife, unless (by a friend personally) introduced to himself, any day, between nine and one, Sundays excepted.
>
> Signed – Martin Van Butchell

This took place about the time of Washington's first inauguration. Time healed the loss, and Van Butchell relegated Mrs. Van Butchell to a closet; then he took a second wife. This lady, like the one in the immortal Thurber cartoon *(51)*, did not object to having a constant reminder of her predecessor about. After Van Butchell died, his son made arrangements with the Board of Curators, and so the embalmed body found its way to the Royal College of Surgeons. Cobbe's account of her appearance 82 years later, quoted by Dobson *(15)*, reports there remained no trace of that once great inherent beauty except a remarkably fine set of teeth, and he regards the over-all state as less than that of innocuous desuetude. A mounted parrot had been placed between her feet in the museum, and unfavorable comparison was made as to state of preservation and appearance of the two. Cobbe ends by saying that the mummy should be burned. And so it was in 1941, involuntarily.

John Sheldon, a surgeon contemporary of the Hunters, also performed by a different process a historic embalming upon a female patient (some say his wife) who died of tuberculosis. He kept his mummy in his bed chamber for a decade or so, and frequently demonstrated the persisting flexibility of her arms and the elasticity of her bosom, to visitors. Time showed that the Hunters' process gave longer lasting esthetic results, though both specimens perished in the same bombing.

In addition to arterial injection, the body cavity is also treated in embalming. Mendelsohn *(38)* from his historical researches reports that Gabriel Clauderius was the first to record an attempt at chemical cavity embalming. In 1769 he used a solution of ammonium chloride and salts of tartar (potassium carbonate) for injection into thoracic and abdominal cavities.

Anatomical experiments continued. Many embalming processes were developed, and the inventors jealously guarded their secrets. The nineteenth century saw a peak of interest in this art. Among the more famous practitioners in that period were Falcony, Gannal, Marquez, Wickersheimer, and Vyvodtsev. This last named

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Russian was so enthusiastic about his method, which employed an aqueous solution containing thymol, glycerol, and alcohol, that he persuaded the Russian government to send him on a tour of Germany, England, America, and Scotland, lecturing on its advantages. He made quite an impression in Philadelphia and again in Edinburgh. He also introduced the use of a pump to force fluid into the arteries. Gannal's and Wickersheimer's celebrated preserving fluids contained arsenous acid among other ingredients. The U. S. Government purchased Wickersheimer's formula for a fancy sum. Both McCurdy and Mendelsohn devoted a section in their treatises to the nature of the embalming fluids of these earlier investigators. Along with this growth of interest and experimentation went an increase in publication which reached a peak in the 19th century.

The effectiveness of the process of that day is indicated in the case of Leopardi, Italy's greatest poet after Dante, who died in Naples in 1837. His devoted friend Ranieri went to extreme pains to have his body embalmed *(39)*, including bribing the police and clergy in order to retain the body in the first place. For his troubles he was shortly thereafter accused of having murdered Leopardi, when the customs police stopped the carriage to inspect the coffin. They found two incisions in the body, made by the doctor and the embalmer. The necessary certificates were produced to acquit Ranieri. Leopardi was buried first at the church of San Vitale in the crypt. The coffin was opened seven years later by Ranieri for 2 hours, when the grave was moved up a level. Leopardi's tomb was declared a national monument by the Italian government in 1897. In 1900 they moved the tomb to a third new site in the same church, and opened the coffin again. "It was then discovered that it had rotted, that the lid had fallen in, and that the bones which had mouldered were mingled with the rotting wood. It was impossible even to find the skull. Of the mortal remains of Leopardi nothing distinguishable was left." In 1939 the casket containing the little that is left of the poet's bones was transferred to the cliff above Mergellina close to the tomb of Virgil. As a note on the effectiveness of present day expert arterial embalming, the recycling of pauper burial grounds has in some cases had to be extended beyond the former 25-year period.

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Modern Era

The modern era begins with Thomas Holmes of Brooklyn, N. Y., who developed a successful technique in connection with shipping home the bodies of soldiers killed in the Civil War battles. He obtained a patent in 1861 for an embalming injection device which was operated by a self-contained hand pump.

A celebrated embalming, the record of which is well detailed *(11, 12, 41)*, is that of Cardinal Donnet, done in 1872. This eminent prelate was also a member of the French Senate for many years, and a figure of national prominence. He is one of the few churchmen who has held this civil office. He rallied the French people during the Franco-Prussian War, and was instrumental in keeping up morale during the siege of Paris. On his death, his clerical associates realized that thousands of his countrymen would wish to pay their last respects, so they sent to the Académie de Médecin for advice and aid, and an outstanding surgeon was dispatched to Bordeaux to perform the embalming. On completion of the process, the body was placed on exhibition upon a catafalque in the cathedral. At the end of the third day it was discovered that a dark spot of necrosis about the size of a dime had developed on one temple. This was touched up with magnesia before people were admitted the next morning to view the body. At the end of the fifth day the black spot had put in a reappearance and grown to the size of a silver dollar. More magnesia was applied. At the end of the sixth day resort had to be made to house paint. For seven days the faithful streamed by to pay homage, and then the last rites and interment were performed.

Despite the officiating surgeon's qualifications and familiarity with substances capable of preserving a corpse, he was unacquainted with either of the pump devices mentioned which were developed in Russia and America to aid dissemination of embalming fluid. The fluid in this case was allowed to flow in by force of gravity, following drainage removal of the blood, and then it was further dispersed through the arterial tree and body by kneading and massage. Think of the foot-pounds of pressure used! By the time this squeezing or squeegee manipulative process had been applied from stem to stern, one intercrural strategic part had become quite

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

turgid and assumed a grossly erectile character. The organ proved so refractory on further manipulation that it had to be slit altitudinally in order to release the pent-up fluid under pressure. *Sic transit. . .*

The date 1878 has been arbitrarily selected for the beginning of the modern era of embalming literature because it marked the publication of Renouard's book, "The Undertaker's Manual" *(42)*. The rapid spread in this country of arterial embalming generally stemmed from his activity. Johnson *(27)* has given a brief biography of Renouard as follows:

Auguste Renouard (1839–1912) was born in New Orleans, La. He attended and graduated from St. Xavier's College and McDowell's Medical College (now St. Louis University) at St. Louis, Mo. Following the outbreak of the Civil War he joined the Confederate forces as a surgeon, and for a time was attached to the staff of Gen. J. E. B. Stuart. After the war, Dr. Renouard returned to St. Louis, where he practiced pharmacy. Subsequently he practiced medicine in Chicago, later losing everything in the great fire of 1871. He then went to Denver, Colo., where he practiced medicine for a time. Later he associated himself with an undertaking and furniture concern, which was commissioned to send the bodies of early settlers back to their homes in various parts of the United States. His knowledge of chemistry and anatomy enabled him to compound fluids similar to those employed for the preservation of anatomical material he formerly used in medical college. The condition of the bodies shipped from Denver to all parts of the United States was such as to excite the curiosity of the receiving undertakers. They communicated with Renouard, and the more progressive made pilgrimages to Denver to receive their early instructions in the first school of embalming in America, established in 1874. This school was situated in the rear of the undertaking establishment. The early students were taken on private cases as assistants, where they were instructed in practical embalming.

Renouard's fame as an instructor spread over the country and his services as such were demanded in the east, where he conducted clinics of embalming instruction in most of the larger cities. He became interested in improving embalming chemicals and instruments, and formulated many embalming fluids and disinfectants. He became author of the first textbook on embalming and funeral directing, in 1876, entitled "The Undertaker's Manual." A second edition was published in 1881. In 1887 he opened the United States College of Embalming in New York City, regarded as the first permanent school of instruction in the field. In 1900 he merged his school with that established by his son, Charles A. Renouard, in 1894. The merged interests were continued under the title of Renouard Training School for Embalmers, which flourishes today under the able directorship of Renouard. (Charles Renouard died in July 1953.) The profession owes much to Auguste Renouard for his many contributions to its progress, for his teachings, research, and writing.

Auguste Renouard received many honors from his students and graduates during his lifetime. The last tribute is in the form of a monument in Greenwood Cemetery, Brooklyn, N. Y., erected by funeral directors and embalmers of the United States and Canada.

Renouard established the first embalming school in the United States in Denver in 1874. His prowess was widely heralded, and he was invited to give clinics to undertakers in all the principal eastern cities. He presently started a school of embalming in New York City; this school continued to operate up to 1953 under his son, Charles Renouard, who died on July 12, 1953.

The literature of embalming is not clear-cut or well organized permitting of an orderly discussion of handbooks, monographs, serials, abstract journals, patents, theses, trade literature, pamphlets, and ephemera. There is no "Handbuch" in this field, although an embalming fluid house publishes the "Expanding Encyclopedia of Mortuary Practice" *(10)* in loose-leaf form. This house organ made its first appearance on June 1, 1923. A complete set is a great rarity. "ESCO Reference Manual of Supplies" *(19)* is a *sine qua non* for the practitioner. This manual was first published in 1934 and has never been revised. The Undertakers Supply Co. has a highly useful catalog *(52)*. Thus, the mortician of 1954 may employ an electromagnetic vibrator for mechanical massage to induce dissemination of fluid, instead of relying upon hand manipulation.

Survey of the Art

Some of the better books may be mentioned that give a survey of the whole art, including much history of embalming. McCurdy's "Embalming and Embalming

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Fluids" *(31)* is fine for historical material up to 1895, and it has an invaluable bibliography. It is still used as a reference standard by the U. S. Patent Office. Johnson *(27)* published in *Casket and Sunnyside* an excellent history of the art and science of embalming, which was reprinted as a 24-page pamphlet. Many embalming schools have used this work to orient their students. It also contains an excellent bibliography. Mendelsohn's book, "Embalming Fluids" *(38)*, written by a chemist with understanding, is factual and debunking when necessary. In addition to treating the chemical aspects, it provides a "digest of jurisdictional regulations governing the composition and potency of embalming fluids in the preparation of bodies for burial and transportation," a "digest of American patents for embalming preparations and processes from 1856 to 1939," miscellaneous useful supplementary tables of data, and a bibliography.

Mendelsohn published a series of splendid historical essays *(20, 33–36)* in 1946 and another on cremation *(37)* in 1951.

Eckels *(18)*, after tracing historical development, gives an introduction to modern embalming, including discussion of anatomical details, technique, instruments, and equipment, a section on treatment of special nonpathogenic cases, a section tabulating pathogenic diseases with their special characteristics, and a reference compend of classified questions and answers for students dealing with anatomy, bacteriology, pathology, chemistry, embalming, funeral management and direction, mortuary law, accounting, psychology and sociology, and funeral service terminology. The reference compend has also been published separately. It concludes with a chapter on shipping rules, giving all state regulations covering transportation of dead bodies, which has been reprinted from the "American Blue Book" (American Funeral Directors). Despite this wealth of information, it is a barbarously written book.

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Table I. Some Colleges, Schools, and Training Centers for Embalming

American Academy of Embalming and Mortuary Research, Inc., 1974 Broadway, New York 23, N. Y. (owned by Pittsburgh Institute of Mortuary Science).
American School of Cemetery Administration, Inc., 3339 Forbes St., Pittsburgh 13, Pa.
Atlanta College of Mortuary Science, 3 Chestnut St., N.W., Atlanta, Ga. (colored only).
Boston School of Anatomy and Embalming, 169 Massachusetts Ave., Boston, Mass.
California College of Mortuary Science, 1920 Marengo St., Los Angeles 33, Calif.
Canadian School of Embalming, 100 College St., Toronto 2, Ont. (Apply for information concerning courses, fees, etc., to Assistant Dean, Banting Institute.)
Cincinnati College of Embalming, 3202 Reading Road, Cincinnati 29, Ohio (founded 1882).
College of Mortuary Science. *See* St. Louis College of Mortuary Science.
Commonwealth College of Science, 102 Drew St., Houston, Tex. (formerly Landig College of Mortuary Science).
Dallas Institute of Mortuary Science, 3906 Worth St., Dallas, Tex. (sponsored by Mortician Supply Co.).
Eckels College of Mortuary Science, 231 North 16th St., Philadelphia 2, Pa. (sponsored by H. S. Eckels & Co.)
John A. Gupton School of Mortuary Science, 2507 West End Ave., Nashville 5, Tenn.
Indiana School of Mortuary Science, 1201 North Capitol Ave., Indianapolis, Ind.
Iowa State University, Iowa City, Iowa (new curriculum in mortuary science).
Kansas City College of Mortuary Science, Inc., 738–40 Washington Blvd., Kansas City, Kan.
Kentucky School of Embalming, 1102 South 2nd St., Louisville, Ky.
Landig College of Mortuary Science. *See* Commonwealth College of Science.
Louisiana State College of Mortuary Science, 2126 South Claiborn Ave., New Orleans 13, La.
McAllister School of Embalming, 305 East 47th St., New York 17, N. Y.
New England Institute of Anatomy, Sanitary Science, and Embalming, 236 Huntington Ave., Boston, Mass. (sponsored by Dodge Chemical Co., also called New England Institute of Mortuary Science)
New York School of Embalming and Restorative Art, Inc., 1295 Madison Ave., New York, N. Y.
Pittsburgh Institute of Mortuary Science, 3337 Forbes St., Pittsburgh 13, Pa.
Postgraduate Institute of Restorative Art, Chicago, Ill.
San Francisco College of Mortuary Science, 1450 Post St., San Francisco 9, Calif. School of Mortuary Administration and School of Embalming Administration, 1170 hours each.
Simmons School of Embalming and Mortuary Science, 2201 South Salina St., Syracuse, N. Y.
Southwest School of Mortuary Science, 3001 Commerce St., Dallas 1, Tex.
St. Louis College of Mortuary Science, 4937 Forest Park Blvd., St. Louis 8, Mo.
Temple University Community College, Eckels Curriculum in Mortuary Science, Philadelphia, Pa.
University of Minnesota, School of Mortuary Science, 4051 Aldrich Ave., N., Minneapolis 14, Minn.
Wayne University School of Mortuary Science, 2817 Grand Blvd., East, Detroit, Mich.
Wisconsin Institute of Mortuary Science, 1205 North Van Buren St., Milwaukee 2, Wis.
Worsham College of Mortuary Science, 620 South Wolcott Ave., Chicago, Ill.

It was Samuel Butler, the author of "The Way of All Flesh," who first pointed out that Wordsworth did not explain the nature of the difference to him, now that Lucy was planted. He then championed the view that Wordsworth welcomed Lucy's death as a release from an irksome engagement, if indeed he had not murdered her.

Training and Schooling

Embalming is a craft trade learned by apprenticeship, rather than a science. Embalmers are in large measure empiricists, taking the solutions devised by the chemists of the fluid houses, and applying them to their work, without knowledge of the constituents or of the chemistry involved.

Today, there are about 25 schools of embalming and mortuary science operating in the United States (Table I). McCurdy *(31)* lists seven in 1895. At least four of these currently operating schools are affiliated with universities—namely, Wayne University College of Mortuary Science, the School of Mortuary Science of the University of Minnesota at Minneapolis, which is a professional school like the School of Pharmacy and now offers a degree (associate in mortuary science) on successful completion of its 2-year curriculum (it also offers refresher courses); Iowa State University's New Curriculum in Mortuary Science, and Temple University Community College, the Eckels Curriculum in Mortuary Science. Table II lists some firms maintaining research staffs.

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Table II. Some Firms in Funeral Industry Maintaining Research Staffs

B and G Chemical Co., St. Paul, Minn.
Century Chemical Co., Columbus, Ohio
Champion Co., 400 Harrison St., Springfield, Ohio
Dodge Chemical Co., 656 Beacon St., Boston, Mass.
H. S. Eckels & Co., Philadelphia, Pa.
Embalmers' Supply Co., Westport, Conn.
Eureka Fluid Works, San Francisco, Calif.
Frigid Co., Chicago, Ill.
Gold Crest Chemical Corp., P.O. Box 1352, Wilmington, Del.
Hizone Products, Wilmette, Ill.
Max Huncke and Co., Brooklyn, N. Y.
Hydrol Chemical Co., 4424–30 Market St., Philadelphia 4, Pa.
L. H. Kellogg Chemical Co., St. Paul, Minn.
G. H. Michel Co., Cleveland, Ohio
Morticians' Supply Co., 409 North Zangs St., Dallas, Tex.
Royal Bond, Inc., 305 South Seventh St., St. Louis, Mo.
Undertakers' Supply Co., 331–9 South Peoria St., Chicago 7, Ill.

New York is one of the few remaining states which licenses as embalmers men who have served apprenticeships but have had no formal training. Many schools of mortuary science require 1 or more years of college before admission. A high school diploma is a prerequisite in all. The legal requirements set by the 48 states to be met for licensure vary considerably, ranging from 1 to 3 years of apprenticeship, and the preparation of from 20 to 50 bodies. The latest tabulation of these data appears annually in the November 15 issue of the *Southern Funeral Director.*

In contrast, McCurdy states that in 1895 only three states—Alabama, Missouri, and Pennsylvania—had enacted laws regulating the embalming business and practitioners.

To prevent an impression that embalming is entirely static and inert, a 1954 *Industrial and Engineering Chemistry* report by Sanders, "After You're Gone" *(45)*, outlines briefly some research by present-day mortuary chemists, particularly those at the University of Minnesota. Pervier is quoted:

We have been engaged in embalming research because of the dearth of literature on the subject, lack of teaching material, plain curiosity, and economics.

That is concise and frank.

Current Literature

The books and monographs in this field may be followed in the usual way via the reviews (they are not reviewed in the U. S. Quarterly Book List), Books in Print, the Cumulative Book Index, the Library of Congress and Armed Forces Medical Library Catalogs, etc., but not necessarily with success. Nor do the mortuary

jurisprudence books all turn up in the collections of distinguished law libraries. It is a matter of persistent searching. The best source of information on new books on embalming and related matters is the trade journals.

Table III. National Trade Associations and Research Institutes

American Association of Colleges of Mortuary Science.
American Cemetery Association.
American Institute of Funeral Directors.
Associated Funeral Directors Service, 5708 McPherson St., St. Louis 12, Mo. (One member to a city. For shipping service purposes, somewhat like American Florists Assoc.)
Casket Manufacturers of America.
Conference of Funeral Service Examining Boards of the U. S. (Annual). Primarily concerned with National Board Examination for Licensing. (Composed of 3 members each from National Association of Colleges of Mortuary Science, American Association of Colleges of Mortuary Science, and National Council on Mortuary Education.)
Cremation Association of America.
Embalming Chemical Manufacturers Association, Inc., 369 Lexington Ave., New York, N. Y. (Organized 1952, and working on a code agreement of principles of business practice.)
Federated Funeral Directors of America.
Funeral Directors and Embalmers Association.
Institute for Mortuary Research, 39 Massachusetts Ave., Detroit 3, Mich. (formed in 1930 by National Funeral Directors Assoc. Became inactive in early 1949.)
Jewish Funeral Directors of America, 2009 North Broad St., Philadelphia 22, Pa.
National Association of Colleges of Mortuary Science (propose to have a national board examination).
National Cemetery Association.
National Concrete Burial Vault Association.
National Council on Mortuary Education.
National Foundation of Funeral Service, 1616 Central Ave., Evanston, Ill. (sponsored by National Selected Morticians. Operates a school of management.)
National Funeral Directors Association, 135 West Wells St., Milwaukee 3, Wis. (founded 1882.)
National Negro Funeral Directors Association, 220 Auburn Ave., Pittsburgh 6, Pa. (founded 1938 and formerly called Progressive Negro Funeral Directors Assoc.)
National Selected Morticians, Inc., 1616 Central Ave., Evanston, Ill. (founded 1917.)
Order of the Golden Rule (Maintains ethical standards in advertising.)
Wilbert Manufacturers Association.

The embalming periodicals on this list seldom publish original work; they are essentially trade association journals (Table VI). They do, however, have an occasional practical article, and such bits as the late Charles Renouard's question and answer column. For instance, the August 1954 issue of *Casket and Sunnyside* has a timely article by F. C. Coleman on the newest problem of embalmers, the radioactive isotope, alongside material on "Funeral Service in South America," and "Modernization of the Winnipeg Mortuary." Some other items from its table of contents may be illuminating:

Psychology in Action, E. A. Martin
Restoration Clinic, E. C. Johnson
The Courts' View of Funeral Service and Its Problems
Mortuary News

The funeral director today must have available a Geiger counter and a lead-lined chamber in which to store radioactive bodies in the interest of self-preservation. No sterile technique and rubber gloves will suffice to protect him from radiation. Groups of embalmers in Texas and Chicago have complained that they were getting more than their share of radioactive bodies to treat. A suggested procedure for performing autopsies on radioactive cadavers has been described lately by Cowing and DeAmicis *(13)*.

The list of journals contains six house organs. McCurdy listed 10 specialty journals in 1895, including the *Furniture and Upholsterer's Journal* of London, and three which were strictly medical science—e.g., *Lancet*. In addition to these journals, 20 to 30 mimeographed monthly news bulletin services are issued by the various state funeral directors societies. Those of New Jersey and Florida are more substantial. Other reputable scientific journals, especially in pathology, occasionally contain articles pertaining to embalming. None is offered for comment here. They can be traced by consulting:

1. The Index Catalog of the Surgeon General's Office, 1st–4th Series inclusive (1883–1940)
2. *Quarterly Cumulative Index Medicus*
3. *Chemical Abstracts*
4. *Current List of Medical Literature* (the last an indifferent source)

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There is talk of creating a really scientific journal in this field to be called the *Journal of Mortuary Science.* In line with the scientific practice which has given us journals called *Blood, Condor, Isis,* and *Auk,* the possibility of *Corpus* may be suggested. There has not been need for a specialized abstract journal or index in this field. Patent literature is included in *Chemical Abstracts;* here it is convenient to start with Mendelsohn's patent survey.

Another book of importance is that of Gebhart *(22)* on funeral costs. A new, accurate, up-to-date edition would be welcomed.

After assimilating the historical art and gaining a clearer concept of practical embalming from the books cited, a chemist might read a study by Schleichter on the combining activity of formaldehyde with tissues *(46).*

Table IV provides a breakdown of books published since 1930. This should be followed by Slocum *(47)* and Spriggs *(48),* with perusal of the books by Calloway, Carden, Renouard, or Johnson for further special pointers (see Table IV). Next, the books on restorative art should be examined. Of these, Adair's book *(1)* is the newest and is written in a breezy, nontechnical style. The Curry book *(14),* which deals with facial reconstruction and fingerprinting the dead, has some special merits.

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Table IV. Classified List of Monographs on Embalming and Related Funerary Phenomena

(Published since 1930)

ANATOMY AND DISSECTION

Apflbach, C. W., "Creating a Better Relationship between the Medical and Mortuary Professions," National Selected Morticians, Chicago, 1935. Reprinted from Proc. 18th annual convention, National Selected Morticians, Toronto, Canada, 1935.

Dhonau, C. O., and Nunnamaker, A. J., "Anatomy and Histology for Embalmers," Dhonau-Nunnamaker Ser., Vol. 1, Casket, New York, 1935; rev. ed. by Dhonau, Britt, and Nunnamaker, 1955.

Nunnamaker, A. J., and Dhonau, C. O., "Dissecting Guide for Embalmers, Outline of Gross Structures of the Human Body," Embalmers Book Co., Cincinnati, 1931.

Saphir, Otto, "Autopsy, Diagnosis, and Technic," 2nd ed., Hoeber, New York, 1946.

Spriggs, A. O., "Plastic Surgery," 4th ed., Champion, Springfield, Ohio, 1946.

BACTERIOLOGY

Wickner and Trayna, "Bacteriology and Hygiene for the Embalmer," 1935.

CHEMISTRY

Deuel, H. J., "Textbook of Chemistry for Students of Embalming," 2nd ed., Master Press, Hollywood, 1935.

McFate, R. P., "Outline of Chemistry, Including Inorganic, Organic, and Physiological Chemistry and Special Notes on Disinfection, Disinfectants, Fumigation, and Embalming Fluids," 3rd ed., Edwards Brothers, Ann Arbor, Mich., 1944.

Pervier, N. C., "Textbook of Chemistry for Embalmers," Burgess, Minneapolis, 1940.

Schleichter, G. M., "Study of the Combining Activity of Formaldehyde with Tissues," thesis, University of Cincinnati, 1939.

EMBALMING

Callaway, C. F., "Textbook of Mortuary Practice. Pathological Condition of and Embalming Treatments for over 150 Diseases, Arranged Alphabetically for Easy Reference," Undertakers Supply Co., Chicago, 1943.

Carder, F. S., 2606 West Ave., Newport News, Va., "Study Guide for Apprentice Embalmers and Funeral Directors," 1948.

Dhonau, C. O., "Manual of Case Analysis," Embalming Book Co., Cincinnati, 1935 (1st ed., 1928).

Johnson, E. C., Worsham College, Chicago, "Manual of Embalming Treatment," 1947.

Landig, R. V., and Garton, W. M., Houston, "Quiz Compend on Mortuary Science," 1947.

Renouard, C. A., and Knox, "Embalmers' Aid and Guide," Casket, New York, 1947.

Slocum, Ray, "Pre-embalming Considerations," Dodge, Boston, 1945.

Spriggs, A. O., "Art and Science of Embalming," 4th ed., Champion Co., Springfield, Ohio, 1946.

FUNERAL DIRECTION AND MANAGEMENT

Apflbach, C. W. *See* anatomy and dissection.

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Proceeding into the funeral aspects, Apflbach *(3)* and Krieger *(28)* are suggested. The book by Martin *(32)*, now in its third edition, is exceptional.

With respect to legal problems, any of the books in that section of Table IV may be recommended. Perhaps those of Street *(49)*, Fellows (for British regulations), or Jackson *(26)* provide the widest range. Jackson has been a stand-by for many years. Street provides a valuable cross index.

One comment on the legal side not given in these books is a law among the Egyptians that bodies of male dead should be delivered at once into the hands of the embalmer, but those of females should wait 3 days in order to avoid the possibility of unseemly experiments. Apparently, heat dissipates more slowly in Egypt.

When criminal considerations arise, attention must also be given to toxicology. Winters *(55)* and Gonzales, Vance, and Helpern *(23)* are suggested, as well as Witthaus *(56)*. Some of the books on medical jurisprudence also have chapters which are applicable—e.g., Robertson *(43)* or Taylor *(50)*.

In this area occasional references appear in the *Medical Legal Journal* (N. Y.), which ceased publication in 1933. A British counterpart by the same title is still current, and contains an Abstract section. There is also a German journal, *Sammlung von Vergiftungs-fällen*, which is concerned with this phase of necropsy. It is sometimes said that the banning of the use of arsenic was a lethal blow from which embalming has never really recovered. Chemists of the fluid houses do not agree. They consider the incorporation of wetting agents in fluids a major advance, improving penetration of the fluid through the tissues. The use of wetting agents would be incompatible with an arsenical fluid.

For any who are worried about mental health, there is a study by Fish *(21)*.

Among the many useful manuals of the United States War Department is one published in 1919 in Philadelphia entitled "Laboratory Methods of the U. S. Army," which devotes some attention to embalming.

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In the pastoral aid subgroup of books Wallis's "The Funeral Encyclopedia" *(53)* is not an encyclopedia in the usual sense, but a collection of sermons appropriate to many final occasions. The Westminster Press of Philadelphia specializes in this class of works. This is the same Wallis who has a recent best-seller on "Epitaphs."

In a section entitled Modern View of (Permanent) Embalming, McCurdy *(31)* says:

Instead of pageants, characteristic of the dwellers of the Nile, the erection of pyramids, the carving of magnificent sarcophagi within the Catacombs of Thebes, at Rome, at Naples, Syracuse, Palermo, or at Athens, or in secret caverns in the mountain's fastness, our modern sepulchral vanity manifests itself in choice epitaphs and monuments, family vaults, or is more sensibly contented with the incinerated remains of the departed as preserved in the urn, instead of in desiccated forms and bitumenized disguises of death.

Furthermore the aesthetic character of all Christian nations and people would protest against the continuance of so extraordinary, if not barbarous, a practice, which made death more hideous to the vision, more repulsive to the sensibilities of a refined and devout soul, than it could possibly be made by the supremest superstition.

Stevenson Smith used to conclude his lectures on the 18th century philosophers—Bishop Berkeley, Hume, and others—by saying that if you wished to meet one face to face, it was still possible because Jeremy Bentham, who taught at the University College, London, left instructions that his body was to be embalmed and kept at the university. This was done, and the remarkable man kept in view there as a reminder to his students and disciples for 50 years or so until one day his head fell off, whereupon he was summarily relegated to a closet. This body is still preserved and can be confronted at the university. It will not be exhibited again, however, until the buildings are restored from wartime destruction.

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Table V. Bibliography of Embalming Literature

Many items recorded here which were first located via secondary sources remain without verification of the usual bibliographic data. Half a loaf is undoubtedly better than none. An apologetic word is consequently offered for lapses in dates, places, publishers, etc., and an invitation issued to erstwhile bloodhounds. It is necessary to go beyond the standard compendia and catalogs of the great libraries. In the second edition of Garrison-Morton the term "embalming" does not appear. It is likewise missing from Sarton's bibliography in his "Guide to the History of Science."

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(1) Augustine (Saint), "De Diversis XII," Sermon 120. Inveighs against the custom of embalming as a pagan practice.

(2) Bible (The), Genesis, Chap. 50, Commentary. Verse 2. "And Joseph commanded his servants the physicians to embalm his father Jacob: and the physicians embalmed Israel." Verse 3. "And 40 days were fulfilled for him; for so are fulfilled the days of those which are embalmed; and the Egyptians mourned for him threescore and ten days . . . " Verse 26. "So Joseph died, being an hundred and ten years old; and they embalmed him and he was put in a coffin in Egypt." Luke, Chap. XII, Verse 2, Chap. XXII, Verse 1. John, Chap. XIX, Verses 39–41.

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Table VI. Check List of Periodicals and Serials of Embalming, Cremation, and Mortuary Science

(Symbols for library holdings correspond to those of the Union List of Serials. Abbreviations DCL, etc., refer to libraries where publications are available. Asterisk indicates house organ. Titles in CAPITAL LETTERS are being published currently.)

(1) *AMERICAN ACADEMY NEWS.* Am. Academy of Embalming and Mortuary Research, New York. Student publication.
(2) *American Art in Stone.* Boston, Mass. 1900–March 1937.
Absorbed by *ART IN BRONZE AND STONE*, March 1937.
(3) *AMERICAN BLUE BOOK OF FUNERAL DIRECTORS.* 1st (1932/33) + biennial.
DLC 4th (1938/39)
6th (1942/43)
11th (latest) (1952/53)
(4) *AMERICAN CEMETERY.* Am. Cemetery Association, Kates-Boylston Publications, New York, N. Y. v. 1, 1929 + M.
(5) *AMERICAN FUNERAL DIRECTOR.* South Bend, Ind.; Grand Rapids, Mich.; New York. Currently published by Kates-Boylston Publications, 607 Fifth Ave., New York, N. Y.
Published 1879–1919 as *Western Undertaker*
v. 1, 1879 + M.
MnU 56, (60–62)
NN (29) – (40, 50–57) +
OCL 55 +
DLC 41–(49), (62–63)
MiGr (45–48)
PP 52 +
(6) *AMERICAN SELECTED FUNERAL DIRECTORS.* Selected Directories, Inc., 120 Liberty St., New York, N. Y. 1932 –
(7) *ASSOCIATION OF AMERICAN CEMETERY SUPERINTENDENTS PROCEEDINGS*, v. 1, 1887 +
B.U.A. MONTHLY (Bulletin of the Undertakers Association). *See NATIONAL FUNERAL DIRECTOR.*
BULLETIN DE LA SOCIÉTÉ POUR PROPAGATION DE L'INCINERATION. See SOCIÉTÉ FOUR PROPAGATION DE L'INCINERATION BULL.
BULLETIN OF THE CASKET MANUFACTURERS' ASSOCIATION OF AMERICA. See CASKET MANUFACTURERS' ASSOCIATION OF AMERICA BULL.
(8) *CALIFORNIA BOARD OF FUNERAL DIRECTORS AND EMBALMERS.* Sacramento, Calif. Report and Directory of funeral directors and embalmers holding certificates under the F.D. and E. Act of the state of California. 1931 + biennial.
(9) *CANADIAN CEMETERY SERVICE AND MEMORIAL CRAFTSMAN.* James O'Hogan and Co., 60 Front St., Toronto 1, Canada. Toronto bi-m. 1930 +.

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

(10) *CANADIAN FUNERAL SERVICE.* James O'Hogan, Jr., ed., 60 Front St., Toronto 1, Canada. v. 1, 1923 + M.
NN 19, 1941 +

(11) *The Casket,* Rochester, N. Y. (devoted to higher education of funeral directors and embalmers.) United with *Sunnyside* January 1925 to form *Casket and Sunnyside.* 1–49, May 1876-D 1924.
DLC 29–49 (1904–24)
DP 49
NN 1–38
NR 11–16
OO (29–30)

(12) *CASKET AND SUNNYSIDE.* Cremation Association of America. v. 1, 1870 + M, 487 Broadway, New York 13, N. Y. 1–54, 1870-D 1924 as *Sunnyside.* v. 5–18 omitted in numbering, and no vols. were numbered 50–54.
19 (1899) as ns. v. 19
DLC 39–46, 48 +
DP 55 +
DSG 4, 19–24
MnU (59–62, 66)
NBuG (63–64)
NN (4), 19 – (33) – (59 – (64) +

(13) *Casket Manufacturers Association of America, Bulletin,* Cincinnati. v. 62 (1918), v. 70–71 published 1920.

(14) *Cemetery Beautiful,* Chicago. v. 1–3, No. 8, July 1917–July 1919.

(15) *COLORED MORTICIANS BULLETIN.* Atlanta College, Atlanta, Ga. M.

(16) *Columbarium, Philadelphia.* Monthly magazine designed to educate people to adopt proper method in disposing of bodies of the dead. v. 2, 1895/96.

(17) *Conference of Cremation Authorities.* London Report of Proceedings. No. 1–10. 1922–31. Title varies. At head of No. 1–3, Cremation Society of England.

(18) *CONFERENCE OF UNDERTAKERS' AND EMBALMERS' EXAMINING BOARDS OF NORTH AMERICA, PROCEEDINGS,* v. 1–14, 1904–1917, 1904–1905 published as Joint Conference of Embalmers Examining Boards and State Board of Health.

(19) *CREMATION ASSOCIATION OF AMERICA, REPORT OF PROCEEDINGS OF THE . . . ANNUAL CONVENTION.* v. 9 + 1925. Earlier reports published in *CASKET,* later in *CASKET AND SUNNYSIDE.*

(20) *CREMATION SOCIETY, PIONEERS OF CREMATION.* London. No. 1, 1936 +

(21) *Cremation Society, Transactions.* London v. 1–46, 1876–1935 | | 1876 and 1879 both numbered v. 1. Previous to April 2, 1930, as *Cremation Society of England.* Continued in *PHAROS.*

(22) *Cremation Society,* London. Why I Believe in Cremation. No. 1–4, 1935/36. | | Conference of Cremation Authorities.

CREMATION SOCIETY OF ENGLAND, See CREMATION SOCIETY, London.

(23) *CREMATORIUM.* Société pour la propagation de l'incineration de la Region de l'Est, Strasbourg. v. 1, 1922 + M. No. 1–17 as *KREMATORIUM.*

*(24) *DE-CE-CO MAGAZINE,* published by Dodge Chemical Co., Boston, Mass. v. 1, 1939 + Bi-Mo. v. 46, No. 4, Aug. 1954.

DEUTSCHE FLAMME. See FLAMMA.

(25) *Eastern States Funeral Director,* Boston. v. 1, 1933 + M. Changed title to *NORTHEAST FUNERAL DIRECTOR* (1946 ?)

(26) *EMBALMERS' MONTHLY AND NATIONAL FUNERAL DIRECTOR,* Sioux City, Iowa; Chicago, v. 1, April 1892 + M. (Union List erroneously reads: Chicago 1, 1891 +).
No general title page and index. v. 31–44 as *Embalmers Monthly.* Absorbed *American Undertaker.* 1903.
CL 42 +
DLC 18– (48–49–65) +
DP 52 +
ICJ 31–46
MnO 45 +
PP 42 +
PPC (11)–(13)

*(27) *THE ESCO MESSENGER,* published by Embalmers' Supply Co., Westport, Conn.

*(28) *EXPANDING ENCYCLOPEDIA OF MORTUARY PRACTICE,* Champion Co., Springfield, Ohio, June 1923 + M.

Federation of Cremation Authorities in Great Britain. See *PHAROS.*

(29) *FEUERBESTATTUNG,* Hanover. v. 1, 1924.

(30) *Feuerbestattung.* Hof. a.S. v. 1–10, No. 12, 1924– March 1934. | |

(31) *FEUERBESTATTUNG. Zeitschrift des Grossdeutschen Verbandes der Feuerbestattungsvereine e.V.;* Mitteilungern der Grossdeutschen Feuerbestattung V. V. a.G., Berlin. v. 1, 1929 + v. 1–6 published as *Zentralblatt fur Feuerbestattung.*

(32) *FLACARA SACRA.* Organ pontru propagarea crematinunsi umane in Romania, Bucaresti. v. 1, 1934– ?

(33) *FLAMMA.* Organ des Luxemburger Feuerbestattungsvereins; organe de la Société luxembourgeoise pour la propagation de l'incineration, Luxemburg, v. 1, March 1932 +

(34) *FLAMMA,* vormals *Deutsche Flamme, Zeitschrift zur Foerderung der Feuerbestattung,* Berlin. v. 1, Nov. 1924 +. v. 1–5, No. 7/8, as *DEUTSCHE FLAMME.*

(35) *Flamme. Zeitschrift zur Foerderung der Feuerbestattung im In- und Ausland,* Berlin. v. 1–50, Sept. 1886 –

(36) *FLAMME.* Verband der deutschen Feuerbestattungvereine in der Tschechoslovakischen Republik. Sitz-Brux. Trautenau. v. 1, 1926 +

(37) *FLAMME.* Verein für Feuerbestattung in Berlin. Berlin v. 1, Sept. 1886. Sept. 1886–Dec. 1887 as *NEUE FLAMME.* v. 4–5 omitted in numbering.

(38) *(THE) FLORIDA FUNERAL DIRECTOR* (Fla. F. D. Assoc.), Aragon Hotel, Office 5, Jacksonville, Fla. v. 1, 1931 + M. (v. 21, No. 5, Sept.–Oct. 1953)

(39) *(THE) FORUM,* official publication, New Jersey. v. 1., Nov. 1934 + M. State Funeral Directors Association, Inc., 217 Shelley Ave., Elizabeth 3, N. J.

(40) *(THE) FUNERAL DIRECTOR.* National Assoc. of Funeral Directors, 57 Doughty St., London, No. 1

(41) *Funeral Directors Association of Missouri.* Proceedings. Ann. DLC v. 19 (1906).

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(44) *FUNERAL DIRECTORS AND EMBALMERS GUIDE AND DIRECTORY,* Amsterdam, New York. Biennial. DLC v. 5–6 (1950/51)

(45) *FUNERAL DIRECTORS' JOURNAL.* Chicago F. D. Journal Co., 77 W. Washington St., Chicago. M. 1910 +

(46) *FUNERAL SERVICE JOURNAL,* Uxbridge, England. v. 1 (1886) + M (incorporating *The Undertakers' and Funeral Directors' Journal)* King and Hutchings, Ltd. Hillingdor Press)

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DLC 2, No. 7–11 (December 1933–June 1934)
3 No. 1–10 (July 1934–September 1935)

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1–34, No. 5, 1894–May 1927 / / v. 1–6, No. 2 as *Canadian Furniture and Upholstering Journal.* v. 18–34, No. 3/5 as *Furniture Journal of Canada.* v. 34, No. 3–5 incorrectly numbered v. 33, No. 3–5. NN (2-4)-20

(50) *Furniture and Upholstering Journal,* London, 1895.

*(51) *Hizone Supplements,* Wilmette, Ill. (Hizone Research Labs.) M? numbered and paged, but not dated.

(52) *HUMANE EMBALMING AND PROGRESSIVE FUNERAL PRACTICE,* bi-mo. Westport, Conn. (v. 14, No. 5, May 1932) Embalmers Supply Co. Issued monthly 1932–40. DLC 1945 ICJ 1932 +

(53) *(THE) IN-FU-DI-AS.* Indiana Funeral Directors Assoc., Hubert Wild, Ex. Secy., 1002 East 36th St., Indianapolis 5, Ind. v. 1, 1937 + Bi-M

(54) *JEWISH SERVICE JOURNAL.* Jewish Funeral Directors of America, Philadelphia 22, Pa. 2009 North Broad St., ed., Bernard Schwartz. Name changed to *JEWISH FUNERAL DIRECTOR* 1953.

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(56) *Joint Conference of Embalmers Examining Boards and State Boards of Health, Proceedings.* (annual) s. 1, 1904 + NNN 2 (1905) Renouard School (1+)

(57) *K.F.D.A. MONTHLY NEWS.* Kansas Funeral Directors Assoc., 417 Capitol Federal Bldg., Topeka, Kan. v. 1, 1938 + M.

KREMATORIUM. See CREMATORIUM.

MASSACHUSETTS BOARD OF REGISTRATION IN EMBALMING. ANNUAL REPORT. No. 1, 1906 +

(58) *MIDCONTINENT MORTICIAN;* Grant Williams, ed., 512 Nicollet Ave., Minneapolis 2, Minn. v. 1, 1931 + Mo. For reliable morticians in the heart of America. MnHi (7) +

(59) *MODERN CEMETERY,* C. H. Sample, ed., 214 South Church St., Rockford, Ill. v. 1, March 1891 + M. 1891–Feb. 1895 as *MODERN CEMETERY.* March 1895–Feb. 1900, 1932 as *PARK AND CEMETERY.* May 1900–1931 *PARK AND CEMETERY AND LANDSCAPE GARDENING.*

(60) *MONUMENTAL NEWS REVIEW,* Monumental News Rev., Inc., 45 Carroll St., Buffalo 3. v. 1, 1889 + M. v. 49, No. 6 omitted in numbering. v. 50, No. 10 never published.

(61) *Mortician,* Chicago. v. 1–4, No. 9, F. 1934– 0.1937 v. 1–4, No. 4, 1934–May, 1937 as *National Mortician. NN*

(62) *MORTICIANS OF THE SOUTHWEST,* Mat Arons, ed., 1313 Patterson St., Dallas, Tex. v. 1, 1947 + M

(63) *MORTUARY MANAGEMENT,* 810 South Robertson Blvd., Los Angeles 35, Calif. v. 1, 1914 + M v. 1–11 published as *Pacific Coast Undertaker*

(64) *MORTUARY SCIENCE,* Evanston, Ill. National Selected Morticians, 1935 + Irr.

(65) *NATIONAL FUNERAL DIRECTOR,* M. (National Assoc. of Fun. Directors, 11 Soho Square, London SW 1) Formerly *B.U.A. MONTHLY*

(66) *National Funeral Directors' Association of America, Proceedings of the Convention.* Chicago, Ill. Annual. v. 1–41 (1882–1922/ /?) 1st (1882)
DLC 24th (1905) 25th (1906) 34th (1915)

(67) *NATIONAL MESSAGE,* National Casket Co., Boston. External organ. Not published during World War II. v. 1, Dec. 1924 Bi-m.

(68) *NATIONAL MORTICIAN. See Mortician.*

(69) *NATIONAL NEGRO FUNERAL DIRECTORS BULLETIN,* 730 East 63rd St., Chicago 37, Ill. Irr.

*(70) *NATIONAL NOTES,* National Casket Co., Boston. v. 26, No. 6 May/June 1954. Internal organ.

(71) *NATIONAL SELECTED MORTICIANS. PROCEEDINGS OF ANNUAL CONVENTION,* Chicago. No. 1, 1917 + ?

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(72) *New England Cremation Society Transactions.* Boston. No. 1–3, 1893–99.

(73) *NORTHEAST FUNERAL DIRECTOR,* 118 Summer St., Boston 10, Mass. Formerly *EASTERN STATES FUNERAL DIRECTOR.*

(74) *OHIO MONUMENT BUILDER,* Monument Builders of Ohio, 240 East Mound St., Columbus 15. 1937 + M.

(75) *Pacific Coast Undertaker.* v. 1–11 (1914–1925). Changed title to *MORTUARY MANAGEMENT* in 1926.

Park and Cemetery and Landscape Gardening. See MODERN CEMETERY.

(76) *PHAROS.* Federation of Cremation Authorities in Great Britain, London. v. 1, Oct. 1935 and Q. Supersedes, in part, *CREMATION SOC. LONDON TRANSACTIONS.*

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PIONEERS OF CREMATION. See Cremation Society.
PROCEEDINGS. See name of organization.
(77) *THE PROFESSIONAL EMBALMER.* Published by Undertakers Supply Co., 331 South Peoria St., Chicago, Ill; 725 Washington Blvd., Los Angeles, Calif. v. 1, 1924 + Bi-Mo? DP v. 17 (1941)–22 (1945); DLC v. 16 (1939)–(19)–23, No. 4 (April, 1948 –(22)–(26)+
REPORT. See name of society.
(78) *SOCIÉTÉ POUR PROPAGATION DE L'INCINERATION BULLETIN.* Paris. No. 1, 1882 +. Name of society varies.
(79) *SOUTHERN FUNERAL DIRECTOR,* 1070 Spring St., Atlanta, Ga. v. 1, 1919 + NN 18, 1928+. DLC 49, No. 2 (August 1943) +
(80) *(The) Sunnyside. See CASKET AND SUNNYSIDE* and *The Undertaker.*
TRANSACTIONS. See name of society.
*(81) *(The) Tru-Tone Mortician,* issued by Morticians' Supply Co., Dallas, Tex.
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(83) *Undertakers Directory.* Annual? 1907– ? Complete list of undertakers in states of Conn., Mass., N. H., R. I., N. J., and Vermont. McCourtie, Springfield, Mass.
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(85) *(De) URN,* Amsterdam. v. 1, Dec. 1924 +
(86) *(The) Urn,* New York. A monthly journal devoted to the interests of cremation. v. 1–4, 1892–95//
(87) *VEREENIGING VOOR FACULTATIEVE LIJKVERBRANDING,* The Hague. *BERICHTEN EN MEDEDEELINGEN.* v. 1, 1875 +
(88) *(De) VLAM,* Amsterdam. v. 1, 1924 +
(89) *(Die) Volksfeuerbestattung,* Vienna. v. 1, No. 1–12, Feb. 1926–Sept. 1927
(90) *(Die) Volksfeuerbestattung,* Berlin. (Organ des Volks–Feuerbestattungs Verein VVag.) v. 1–16, 1918–33//?
(91) *Western Undertaker.* v. 1-40 (1879-1918). Changed title to *American Funeral Director* in 1919.
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American Undertaker. Boston. v. 1–5, No. 2. Jan. 1900–March 1904// merged into *Embalmer's Monthly* 1903.
Canadian Casket
(The) Embalmer
(The) National Undertaker
Our Paper
Progression. Rochester, N. Y.
Shadyside
(The) Shroud. Chicago and N. Y. v. 1, No. 1, 1880–85? // ed., Richard McGowan.
(The) Shroud. Chicago and N. Y. v. 1, No. 1, 1880–85? // ed., Richard McGowan. N. Y., 1871, ed., Henry E. Taylor. (First trade paper in field.) Changed title 1872 to *Sunnyside.*

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Antibiotic Literature File for Chemists

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A simple punch-card file has been established to make the current antibiotic literature useful to research personnel engaged in isolation and identification of antibiotics. The coding outline is practical and adapted to the needs of people using the file. A similar file should be useful with the literature of other substances which are not easily classified by the conventional chemical coding system.

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Various methods are currently available for comparison of new with known antibiotics. Comparison on the basis of antibacterial spectrum lacks specificity. The results of physicochemical tests on the antibiotic samples can be compared, but such a procedure is expensive and not adapted to a large number of samples. Comparison of paper chromatography results is probably the most routinely used method of identification. While this method is generally satisfactory, it too is not foolproof because of the influence of various factors on the location of zones. The fact that actual samples of the known antibiotics must be obtained for comparison is its chief limitation.

The antibiotic literature file described in this paper is an attempt to make the scientific literature useful as a tool for comparison of antibiotics, supplementing the methods mentioned above. Such a file does not permit final identification, but it helps to narrow down the number of closely related substances. One of its chief advantages is the opportunity for comparison when actual samples are not available.

The establishment of the file was justified by the continuing importance of antibiotic research, the great number of antibiotics reported, and the potential prevention of unnecessary laboratory work.

The file was originally set up as a name file to supplement Baron's "Handbook of Antibiotics" *(1)*. This system was adequate as a collection of information, but, as the file grew, it became too time-consuming to read each card in order to compare properties listed with those of laboratory substances. The punched-card system was started so that antibiotics with specific groups of properties could be separated for comparison. Machine-sorted cards were adopted because the equipment was readily available, and the number of punches desired was greater than could be handled on an edge-punched card, using a simple direct code.

Coding Outline

The coding outline finally adopted (Table I) was worked out after much consultation with members of the biochemical and microbiological research departments. The primary consideration was usefulness for comparison purposes; many sections of the outline look peculiar when examined from a taxonomic or medical viewpoint. Undoubtedly many people will disagree with this arrangement, even for comparison, but agreement is not necessary for use, as long as the user knows what is included in the various sections.

The procedure for dealing with the antibiotic salts was one of the most difficult problems in organizing the physicochemical part of the outline. The free form was selected in order to have the broadest and most consistent basis for comparison, even though the free form is not often used for biological testing. A simple salt is recorded only when no chemical information can be found for the free form. However, it was undesirable to have sulfates, for example, coinciding with antibiotics containing organic sulfur when the cards were searched, or to have salts coinciding with

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neutral substances. Therefore exceptions were made as noted in the sections on elements and chemical nature.

Table I. Coding Outline

Physicochemical Data

Outline	*Code No.*	*Notes*
File No.	Col. 0–5	
I. Chemical purity	Col. 6	Crystalline substance is considered pure. Substance is reported as crystalline if any salts are crystalline. Noncrystalline substance is considered pure if reported pure or 50%+ pure.
A. Pure	11	
1. Crystalline	1	
B. Impure	12	
II. Elements (No. of atoms)		In columns 7-9, code No. 12 means that analysis figures for element are given but No. of atoms is not given.
A. Carbon	Col. 7	
1. 0–10	1	
2. 10–15	2	
3. 15–20	3	
4. 20–25	4	
5. 25–30	5	
6. 30–35	6	
7. 35–40	7	
8. 40+	8	
9. Percentages	12	
B. Oxygen	Col. 8	
1. 0–8	1	
2. 8–15	2	
3. 15+	3	
4. Percentages	12	
C. Nitrogen	Col. 9	
1. 0–5	1	
2. 5–10	2	
3. 10–15	3	
4. 15+	4	
5. Percentages	12	
D. Other	Col. 10	Elements not punched when antibiotic is reported in form of salt containing them.
1. Sulfur	0	
2. Chlorine	1	
3. Bromine	2	
4. Iodine	3	
5. Miscellaneous	4	
III. Molecular weight	Col. 11	Experimental, not theoretical, values reported.
A. 0–100	0	
B. 100–200	1	
C. 200–300	2	
D. 300–400	3	
E. 400–500	4	
F. 500–600	5	
G. 600–700	6	
H. 700–800	7	
I. 800–900	8	
J. 900–1000	9	
K. 1000+	11	
	Col. 12	Blank.
IV. Melting point ° C.		Melting points of salts not punched unless antibiotic is reported in salt form only.
A. 0–50	0	
B. 50–100	1	
C. 100–150	2	
D. 150–200	3	
E. 200–250	4	
F. 250–300	5	
G. 300+	6	
V. Optical rotation		
A. Water	Col. 14	
1. Positive	11	
2. Negative	12	
B. Alcohol	Col. 15	
1. Positive	11	
2. Negative	12	
C. Chloroform	Col. 16	
1. Positive	11	
2. Negative	12	

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Physicochemical Data

Outline	*Code No.*	*Notes*
VI. Optical spectrum	Col. 17	All maxima reported under all conditions.
A. 200–220	0	
B. 220–230	1	
C. 230–240	2	
D. 240–250	3	
E. 250–260	4	
F. 260–270	5	
G. 270–280	6	
H. 280–290	7	
I. 290–300	8	
J. 300–320	9	
K. 320–340	Col. 18 0	
L. 340–360	1	
M. 360–380	2	
N. 380–400	3	
O. 400–450	4	
P. 450–500	5	
Q. 500–550	6	
R. 550–600	7	
S. 600–700	8	
T. 700+	9	
VII. Infrared spectrum	Col. 18 12	Punch indicates that information is given in articles cited on master card.
VIII. Chemical nature	Col. 19	
A. Acidic	0	To be interpreted as "salt of acid" when salt form of antibiotic is coded.
1. Mono-acid, $pK_a < 5.0$		
2. Mono-acid, $pK_a > 5.0$		
3. Polyacidic		
B. Basic	4	To be interpreted as "salt of base" when salt form of antibiotic is coded.
1. Mono-base, $pK_a < 9.0$	5	
2. Mono-base, $pK_a > 9.0$	6	
3. Polybasic		
C. Neutral	8	
D. Amphoteric	9	
IX. Color	Col. 20	Color of crystals is coded, if crystalline; if not, color of powder, etc. If no color is given for free form, color of a simple salt such as sodium salt is coded. When salt form of antibiotic is coded, color of that salt is coded. Color of highly colored salts (helianthates, diazo salts, reineckates, salts with sulfonic acid dyes) is never coded. When antibiotic has been described as yellow-orange, orange-red, etc., second-named color is coded—e.g., orange for yellow-orange, red for orange-red.
A. White or colorless	0	
B. Violet	1	
C. Yellow	2	
D. Orange	3	
E. Red	4	
F. Other	5	
X. Solubility	Col. 21	Solubility of free form only is coded. If salt form of antibiotic is coded, solubility of that salt is coded. Col. 21, 0 does not include solubility in acid or alk. H_2O. Col. 21, 5 includes methanol, ethanol, propanol, acetone, dioxane, and acetic acid. All plant products, including fungus mycelia, are coded under Col. 21, 8 regardless of solvent used. An extracting solvent is coded in its proper solubility group, even if antibiotic is not soluble in solvent under standard conditions.
A. Water-soluble	0	
B. Organic solvent-soluble	4	
1. Water-miscible	5	
2. Water-immiscible	8	
	Col. 22	Blank
XI. Stability	Col. 23	
A. Acid stable	0	Any $pH < 7.0$
1. Room temp.	1	
2. Heat (10 min. at 70°)	2	
B. Alkali stable	4	Any $pH > 7.0$
1. Room temp.	5	
2. Heat (10 min. at 70°)	6	
C. Thermostable (10 min. at 70°)	8	Used when pH conditions are not given.
Stability data given, but not in any of above terms	12	Antibiotics which retain 75% of their activity after exposure to stated conditions are considered stable. Stability of free form is coded, even if there is a more stable salt. If salt form of antibiotic is coded, stability of that salt is coded.

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Table I Continued

Physicochemical Data

Outline	Code No.	Notes
XII. Qualitative tests		
A. Molisch	Col. 24 0	
B. Reducing test	1	Includes Benedict, Fehling, Tollens silver mirror. Qual. tests coded only when reported—e.g., peptide antibiotic is not coded for biuret test if that test is not reported in article.
C. Seliwanoff	2	
D. Tollens orcinol	3	
E. Biuret	4	
F. Ninhydrin	5	
G. Sakaguchi	6	
H. Xanthoproteic	7	
I. Ehrlich	8	
J. Ferric chloride	9	
K. Folin-Ciocalteu	Col. 25 0	
L. Periodate	1	
M. Iodoform	2	
N. Schiff	3	
O. Permanganate	4	
P. Bromine in CCl_4	5	
Q. Liebermann-Burchard	6	
R. Fluorescein	7	
S. Liebermann's nitroso	8	
T. Maltol	Col. 26 0	
U. Elson-Morgan	1	
V. Hydroxamic acid	2	
XIII. Chemical structure	Col. 27	
A. Polypeptide	0	
B. Polysaccharide	3	
C. Quinone	6	
Structure completely known	12	
	Col. 28	Blank
XIV. Degradation products	Col. 29 12	Coded when partial structure known. This column not coded when complete chemical structure is known.
XV. Inactivating agents	Col. 30	
A. Serum	1	Includes complete or partial inactivation or reversal. Refers to chemical compounds only, not to operations performed on antibiotic (such as hydrogenation), or to factors connected with stability (such as exposure to moist air).
B. Other	2	
	Col. 31–44	Blank

Biological Data, in vitro

Outline	Code No.	Notes
Source of Antibiotic		In vitro spectrum
I. Actinomycetes	Col. 45	Pure antibiotic: quantity required for complete antibiotics must fall below coding limit for each group in order to be coded.
A. Streptomyces	1	
B. Nocardia	2	
C. Micromonospora	3	
II. Bacteria	Col. 46 0	Impure antibiotics: Groups coded according to author's statement of activity, regardless of whether quantity required is below coding limit.
III. Other fungi	5	
IV. Algae	Col. 47 0	
V. Lichens	5	
VI. Animal	Col. 48 0	Quantitative data: Quantities given in γ/ml. or units which can be converted to γ/ml.
VII. Higher plants	1	No quantitative data: Reports of activity in terms which cannot be converted to γ/ml. Groups coded according to author's statement of activity, for both pure and impure antibiotics.
In vitro spectrum		
I. Gram positive	Col. 49	Coding limit: 10 γ/ml. for complete inhibition.
A. Cocci	0	
B. Other gram positive	1	
C. Quantitative data	11	
D. No quantitative data	12	
II. Gram negative	Col. 50	Coding limit: 25 γ/ml. for complete inhibition.
A. Nonindicative of gram negative activity	0	
B. Indicative of gram-negative activity	5	Includes *Escherichia, Aerobacter, Pseudomonas, Proteus, Salmonella, Shigella,* Bodenheimer's bacillus, and *Vibrio* species.
C. Quantitative data	11	
D. No quantitative data	12	

Biological Data, in vitro

Outline	*Code No.*	*Notes*
III. Mycobacteria	Col. 51	Coding limit: γ/ml. from complete inhibition.
A. Pathogenic for man	0	
B. Other	1	
C. Quantitative data	11	
D. No quantitative data	12	
IV. Fungi	Col. 52	
A. Other fungi	0	Coding limit: 25 γ/ml. for complete inhibition.
B. Medically interesting	4	Includes fungi causing coccidiomycosis, histoplasmosis, blastomycosis, cryptococcosis, actinomycosis, and moniliasis.
C. Quantitative data	11	
D. No quantitative data	12	
V. Parasites	Col. 53	No coding limit. Groups coded according to author's statement of activity.
A. Amebae	1	
B. Spirochetes	2	
C. Hemoflagellates	3	
D. Trichomonads	4	
E. Ciliates	5	
F. Helminths	6	
	Col. 54	Blank
	Col. 55	Blank

Biological Data, in vivo

Outline	*Code No.*	*Notes*
Route of administration of antibiotic		Applies to entire in vivo spectrum—e.g., if antibiotic is effective orally against any group it is coded under Col. 56, 11.
1. Oral	Col. 56 11	
2. Parenteral	12	
3. Topical	Col. 57 11	
In vivo spectrum		In vivo spectrum
I. Gram positive	Col. 56	No coding limit. Groups coded according to author's statement of activity. In vivo includes *in ovo*.
A. Cocci	0	
B. Other gram positive	1	
II. Gram negative	Col. 57	
A. Nonindicative of gram-negative activity	0	
B. Indicative of gram-negative activity	5	
III. Mycobacteria	Col. 58	
A. Pathogenic for man	0	
B. Other	1	
IV. Fungi	Col. 59	
A. Other fungi	0	
B. Medically interesting	4	
V. Parasites		
A. Protozoa		
1. Amebae	Col. 60 0	
2. Spirochetes	1	
3. Hemoflagellates	4	
4. Trichomonads	7	
5. *Plasmodium*	Col. 61 0	
6. *Toxoplasma*	1	
7. *Anaplasma*	4	
8. Ciliates	5	
9. Coccidia	8	
B. Helminths	Col. 62	
1. Nematoda	1	
2. Trematoda	4	
3. Cestoda	7	
VI. Tumor	Col. 63 12	
VII. Arthropods	Col. 64	
A. Insecta	0	
B. Arachnida	1	
Antiviral spectrum (in vivo and/or in vitro)		Antiviral spectrum. No coding limit. Groups coded according to author's statement of activity.
I. Dermotropic	Col. 65 0	
II. Neurotropic	5	
III. Viscerotropic	Col. 66 0	
IV. Pneumotropic	5	

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Table I Continued

Biological Data, in vivo

Outline	*Code No.*	*Notes*
V. Pantropic	Col. 67 0	
VI. Microbial	5	
A. Bacteria	6	
B. Actinomycetes	9	
VII. *Rickettsia*	Col. 68 11	
VIII. Plant	12	Includes food preservation, fermentation uses, rat repellent, insecticides, spermaticidal activity.
Nontherapeutic uses	Col. 69 12	
I. Growth promotion	0	
	Col. 70	Blank.
	Col. 71	Blank.
Toxicity		Toxicity.
I. Oral	Col. 72	Delayed toxicity (3 under Col. 72–75). Death 72 hours or more following single injection. Other data (4 under Col. 72–75). Includes chronic toxicity by route used, antibiotic stated to be "toxic" or "nontoxic" by route used, LD_{50} values on animals other than mice by route used, expressions of toxicity in terms other than LD_{50} values by route used.
A. LD_{50} = 0–500 mg./kg.	1	
B. LD_{50} = 500 mg./kg.+	2	
C. Delayed toxicity	3	
D. Other data	4	
II. Intravenous	Col. 73	
A. LD_{50} = 0–50 mg./kg.	1	
B. LD_{50} = 50 mg./kg.+	2	
C. Delayed toxicity	3	
D. Other data	4	
III. Intraperitoneal	Col. 74	
A. LD_{50} = 0–50 mg./kg.	1	
B. LD_{50} = 50 mg./kg.+	2	
C. Delayed toxicity	3	
D. Other data	4	
IV. Subcutaneous	Col. 75	
A. LD_{50} = 0–200 mg./kg.	1	
B. LD_{50} = 200 mg./kg.+	2	
C. Delayed toxicity	3	
D. Other data	4	
V. Other data	Col. 76	
A. Other routes of administration	0	
B. "Nontoxic" no data	3	
C. "Toxic" no data	4	
D. Topical application	5	
E. Red blood cell hemolysis and/or blood dyscrasias	6	
F. Phytotoxicity	7	Data given, irrespective of whether antibiotic is toxic or nontoxic to plants.
	Col. 77–80	Blank.

The coding outline makes use of positive results only; negative results are not coded or reported on the master card. Because the file was established as a guide to the appropriate literature references, not as a substitute for them, it was felt that the person really interested in information on an antibiotic would consult the original references. Negative results would be found in these references. The emphasis on positive results is an obvious limitation when, for example, the effectiveness of an antibiotic against a group of microorganisms is disputed. The group will be coded if one positive literature reference is found, although there may be several negative references. Here again, referral to the original reference will usually reveal the other side of the picture. Information is not evaluated when it is put into the file. It is simply recorded as given by the author, and evaluation is left to the user of the file. A more critical system would encounter the usual differences of opinion, demand more time, and require personnel with a greater degree of scientific training than was warranted.

Establishment of a quantitative basis of comparison for biological in vitro data was undoubtedly the most difficult part of the coding outline development. As no two authors agree on a definition of "activity," some standard was absolutely necessary in order to compare the antibiotic activities. The system used is recorded with the "in vitro spectrum" section of the coding outline. The coding limits are very liberal because of the decision that it was better to err on the side of inclusiveness

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In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

than of exclusiveness. More generous conditions were allowed for impure antibiotics because further purification might bring the activity within the significant range.

The practical character of the coding outline is most apparent in the groupings found in the gram-negative and fungi sections. The division into groups indicative and nonindicative of gram-negative activity was made on the basis of the characteristic pattern of sensitivity of the organisms toward known antibiotics. Indicative gram negatives are those organisms not sensitive to antibiotics which are predominantly or solely effective against gram-positive organisms—for example, *E. coli* is not sensitive to penicillin. Organisms have been put in the nonindicative gram-negative group either because they are frequently sensitive to antibiotics which are predominantly effective against gram-positive organisms, or because they are not tested often enough to determine their "indicativeness." The sensitivity of *Neisseria gonorrhoeae* to penicillin is a practical example of the nonindicative group. This activity does not serve to characterize penicillin as an antibiotic effective against gram-negative organisms. The fungi considered medically interesting in this outline. However, a real effort is made to record clinical effectiveness against mycobacsonnel. Complete agreement will never be reached on any such outline, but agreement is not necessary for use if the groupings are adequately defined.

As no attempt was made to cover the clinical literature adequately, the distinction between in vivo activity in animals and in man is not made in the coding outline. However, a real effort is made to record clinical effectiveness against mycobacteria, fungi, parasites, and tumors on the master card.

IBM Card and Code Arrangement

The standard 7⅜ × 3¼ inch, 80-column IBM card (No. 5081) is used, with no special printing. As shown in the coding outline, a simple, direct code which utilizes the numbers available in each of the 80 columns is used. Twelve punches are available in each column when the numbers 0 to 9 and the overpunches 11 and 12 are used. Twelve is the upper punch in the blank section of the card; 11 is below it.

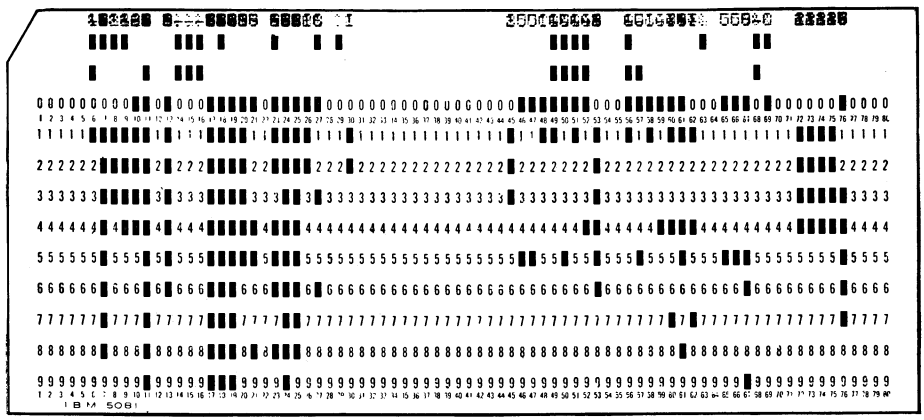


Figure 1. Standard IBM card

The possibilities for expansion of the code are indicated both in the coding outline and in the card reproduction (Figure 1). All numbers currently being used are punched; the unpunched areas show the space available for expansion. It is, of course, very difficult to predict just where expansion will be needed. An effort has been made to leave columns free in strategic places, and to leave space within columns where further subdivision may become desirable.

Master Card

Definite information and references supporting the groups punched on the IBM card are contained on the master cards (Figures 2 to 6), which are related to the proper IBM card through the corresponding file number. Each card is a different color for quick location in the files. The "Biological Data—in vivo" master card is not needed for a great many antibiotics.

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

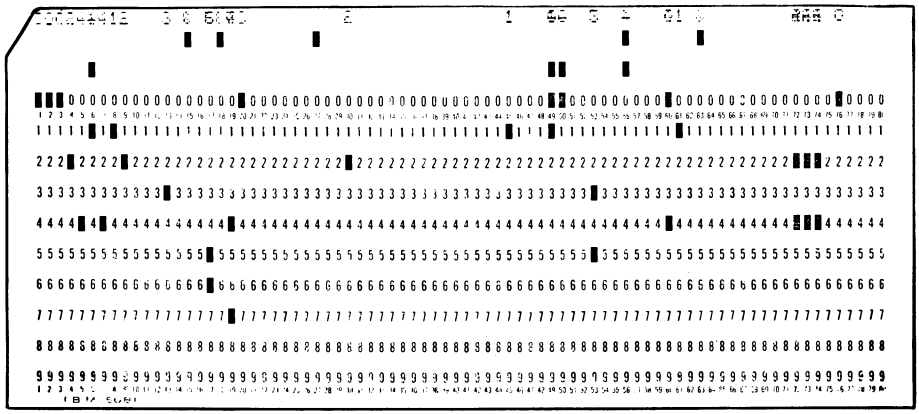


Figure 2. IBM card

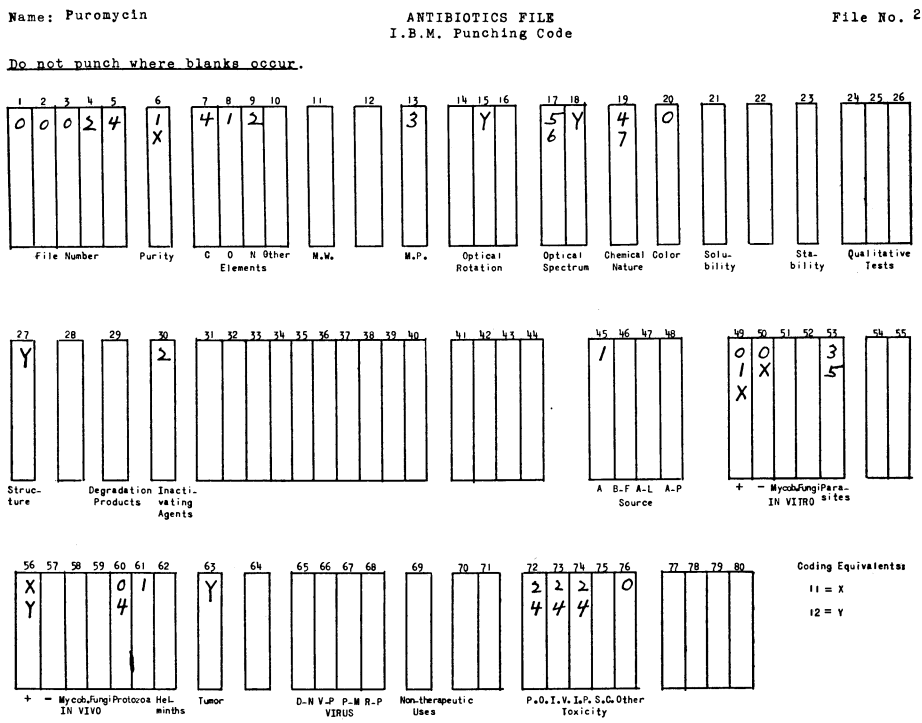
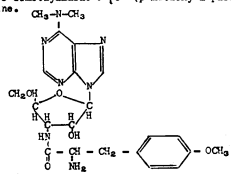


Figure 3. Punching code sheet

NAME Puromycin — ANTIBIOTICS FILE — FILE No 24

DATA	PHYSICOCHEMICAL DATA	REFERENCES
PURITY		
CRYSTALS Crystallized in the form of various acid salts and as the free base.		Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952.
EMPIRICAL FORMULA $C_{22}H_{29}N_7O_5$ OTHER ANALYSIS (%): C. H. O. N.		Waller, C.W. J. Am. chem. soc. 75:2025, 1953.
MOLECULAR WEIGHT		
MELTING POINT (°C.) 175.5-177° (uncorrected)		Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952.
OPTICAL ROTATION: H_2O: ALCOHOL $[\alpha]_D^{26} = -11°$ CHLOROFORM		Waller, C.W. J. Am. chem. soc. 75:2025, 1953.
OPTICAL SPECTRUM MAX. (mμ) $E^{1\%}_{1cm}$ pH 275 20,300 0.1 N NaOH 267.5 19,500 0.1 N HCl		Waller, C.W. J. Am. chem. soc. 75:2025, 1953.
INFRARED Data given.		Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952.
CHEMICAL NATURE A diacidic base.		Waller, C.W. J. Am. chem. soc. 75:2025, 1953.
COLOR Colorless		Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952.
SOLUBILITY		
STABILITY		
TESTS AND REACTIONS		

CHEMICAL STRUCTURE AND DEGRADATION PRODUCTS Group analyses show the presence of one amino group (Van Slyke), one methoxyl group, two N-methyl groups, and five-active hydrogens. Infrared band indicates a carbonyl group. Degradation products: 6-dimethylamino purine, O-methyl-L-tyrosine, D-3-aminoribose.
(2) D-3-aminoribose identified by comparison with a synthetic sample. This is the first known 3-amino sugar and first known aminopentose to exist in a natural source.
(3)Derivatives: crystalline "aminonucleoside", 6-dimethylamino-9-(3'-amino-β-D-ribofuranosyl)-purine. A variety of amino acids such as L-phenylalanine, L-tyrosine, L-lysine, L-tryptophan, L-leucine, β-alanine, glycine and p-methoxy-L-phenylalanyl-glycine were coupled with the "aminonucleoside" to give analogs of puromycin.
(4) Total synthesis of puromycin from D-xylose.
(5)Structure: 6-dimethylamino-9-[3'-(p-methoxy-L-phenylalanylamino)-β-D-ribo-furanosyl]-purine.
(6) Structure:



(7) Synthetic studies. I. Synthesis of 6-dimethylaminopurine, an hydrolytic fragment. II. The position of glycosidation on the 6-dimethylaminopurine moiety. III. Synthesis of 3-amino-D-ribose. IV. Glucosyl derivatives of 6-dimethylaminopurine. V. 6-dimethylamino-9-(2'acetamino-β-D-glucopyranosyl)-purine. VI. Analogs of 6-dimethylaminopurine.

NAME Puromycin
Waller, C.W. J. Am. chem. soc. 75:2025, 1953.
(2)Baker, B.R. Ibid., 75:3864-5, 1953.
(3)Baker, B.R. Ibid., 76:2038, 1954.
(4)Baker, B.R. Ibid., 76:4044-45, 1954.
(5)Baker, B.R. Abstracts, ACS 126th meeting, Sept. 12-17, 1954, p. 13N.
(6)Hutchings, B.L. Ibid., p. 13N.
(7)Baker, B.R. J. org. chem. 19:631-37, 638-45, 645-69, 1780-85, 1786-92, 1793-1801, 1954.

INACTIVATING AGENTS. Activity destroyed by acid hydrolysis.
(2)Activity reduced by adenine sulfate if given to animals in considerably larger amounts than the antibiotic.
(3)Various substituted purines reverse the activity of puromycin and an amino-nucleoside analog (24841) against Trypanosoma equiperdum in vivo.

Waller, C.W. J. Am. chem. soc. 75:2025, 1953.
(2)Agosin, M. Antibiotics & chemotherapy 4:524-32, 1954.
(3)Hewitt, R.I. Antibiotics & chemotherapy 4:1222-27, 1954.

MISCELLANEOUS Company: Lederle
(2)Puromycin is the chemical generic name of the antibiotic formerly called achromycin.

Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952. (2)Hesseltine, C.W. Mycologia 46:75-23, 1954.

BARON _____ KAREL _____ PRODUCT FILE X ABSTRACT FILE

Figure 4. Master card for physicochemical data
Upper. Front
Lower. Reverse

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

NAME Puromycin

ANTIBIOTICS FILE
BIOLOGICAL DATA — *IN VITRO*

FILE No 24

DATA	REFERENCES
SOURCE Streptomyces albo-niger, n. sp.	Hesseltine, C.W. Mycologia 46:16-23, 1954.
IN VITRO — GRAM POSITIVE COCCI Staphylococcus spp., 8, Sarcina lutea, 2 γ/ml. (-HCl)	Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952.
IN VITRO — GRAM POSITIVE OTHER Bacillus spp., 5-8 γ/ml. (-HCl)	Porter, J.N. Antibiotics & chemotherapy 2:409-10, 1952.
IN VITRO — GRAM NEGATIVE NON-INDICATIVE Klebsiella pneumoniae, 5 γ/ml. (-HCl)	
IN VITRO — GRAM NEGATIVE INDICATIVE	
IN VITRO — MYCOBACTERIA PATHOGENIC FOR MAN	
IN VITRO — MYCOBACTERIA OTHER	
IN VITRO — FUNGI OTHER	
IN VITRO — FUNGI MEDICAL INTEREST	
IN VITRO — PARASITES Trypanosoma cruzi, 25 γ/ml. (2)Activity of "aminonucleoside" against Trypanosoma equiperdum was increased 3-4 fold over that of puromycin itself. (3) Tetrahymena pyriformis.	Hewitt, R.I. Am. j. trop. med. & hyg. 2:254-66, 1953. (2)Baker, B.R. J. Am. chem. soc. 76:2038, 1954. (3)Bortle, L. Antibiotics annual, 1954-55
TOXICITY — ORAL LD_{50}(MICE) = 678 mg/kg. (2)LD_{50}(guinea pigs) = 520 mg/kg.	NAME Puromycin Hewitt, R.I. Am. j. trop. med. & hyg. 2:254-66, 1953. (2)Taylor, D.J. J. Am. chem. soc. 76:4497, 1954.
TOXICITY — INTRAVENOUS LD_{50}(MICE) = 360 mg/kg. Evidence of kidney damage after repeated administration of 25-100 mg/kg. parenterally to rats for from 1-4 weeks.	Hewitt, R.I. Am. j. trop. med. & hyg. 2:254-66, 1953.
TOXICITY — INTRAPERITONEAL LD_{50}(MICE) = 520 mg/kg. (2)LD_{50}(guinea pigs) = 287 mg/kg.	Hewitt, R.I. Am. j. trop. med. & hyg. 2:254-66, 1953. (2)Antibiotics annual, 1954-55
TOXICITY — SUBCUTANEOUS LD_{50}(MICE) =	
TOXICITY — OTHER LD_{50}(guinea pigs) = 202 mg/kg., i.m.	Antibiotics annual, 1954-55
MISCELLANEOUS Possible mode of action: somewhat inhibits in vitro the overall carbohydrate metabolism of T. equiperdum. Its aminonucleoside (an active component) inhibits primarily the O_2 consumption and pyruvate production. Effect of adenine sulfate indicates that the killing mechanism involves purine metabolism rather than carbohydrate metabolism. (2)Suggested that the antibiotic is an antimetabolite of adenine and/or its analogs, and affects T. equiperdum by interfering with purine metabolism and the synthesis of nucleic acids or nucleoproteins.	Agosin, M. Antibiotics & chemotherapy 4:624-32, 1954. (2)Hewitt, R.I. Antibiotics & chemotherapy 4:1222-27, 1954.

BARON _____, KAREL _____ PRODUCT FILE X ABSTRACT FILE

Figure 5. Master card for biological data in vitro
Upper. Front
Lower. Reverse

NAME Puromycin

ANTIBIOTICS FILE
BIOLOGICAL DATA – *IN VIVO*

FILE No. 24

DATA	REFERENCES
ROUTE oral, parenteral	Hewitt, R.I. Am. J. trop. med. & hyg. 2:254-66, 1953.
IN VIVO — GRAM POSITIVE: COCCI:	
OTHER:	
GRAM NEGATIVE: NON-INDICATIVE:	
INDICATIVE:	
MYCOBACTERIA: PATHOGENIC FOR MAN:	
OTHER:	
FUNGI: OTHER:	
MEDICAL INTEREST:	
PARASITES: PROTOZOA: Trypanosoma equiperdum in mice and rabbits, orally and parenterally. T. cruzi in mice, orally and parenterally. (2)Toxoplasma gondii in mice, orally (prolongation of life). (3)Endamoeba histolytica in guinea pigs, 5.40 mg. free base/kg. body weight.	Hewitt, R.I. Am. J. trop. med. & hyg. 2:254-66, 1953. (2)Eyles, D.E. Antibiotics & chemotherapy 4:649-52, 1954. (3)Taylor, D.J. J. Am. chem. soc. 75:4497, 1954.
HELMINTHS:	

NS-1203-E

NAME Puromycin

TUMOR Appreciable activity found against a glioblastoma cultivated in the chick embryo and a mammary adenocarcinoma of the C3H mouse. (2)"Aminonucleoside" highly effective against transplanted mammary adenocarcinoma of C3H mouse, much more active than puromycin itself.	Troy, W. Antibiotics annual, 1953-54, pp. 186-90. (2)Baker, B.R. J. Am. chem. soc. 75:2838, 1954.
VIRUS in vivo and or in vitro — DERMOTROPIC	
NEUROTROPIC	
VISCEROTROPIC	
PNEUMOTROPIC	
PANTROPIC	
MICROBIAL:	
RICKETTSIA:	
PLANT:	
NONTHERAPEUTIC USES:	

Figure 6. Master card for biological data in vivo
Upper. Front
Lower. Reverse

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

No attempt has been made to make the file a complete source of literature references on each antibiotic. The most recent data are entered when the antibiotic is first recorded. After that, references for a specific property are recorded only when they contain new information or corrections of previous data. This procedure is modified for biological data, in that only one set of figures, usually that given when the antibiotic is first reported, is recorded for the quantitative in vitro spectrum. It would be impossible to record the different effective levels reported by various investigators. Some representative organisms in the groups inhibited are listed, but the original article must be consulted to obtain the complete spectrum. Only one reference is necessary in order to establish activity against a coding group. Subsequent references showing activity against the same group are not recorded, even though they contain information on different species within the group. This fact is particularly important in the in vivo and antiviral spectrum sections. The organisms and viruses listed in the various coding groups are not necessarily the only ones susceptible in each group. In actual practice, listing of in vivo and antiviral activity is complete for little known antibiotics, but less adequate for the better known ones. The basis for this procedure is the fact that the primary purpose of the coding system is chemical comparison. No attempt has been made to give complete biological data but merely an idea of groups against which activity has been found.

The names "Baron" and "Karel" on the master cards refer to Baron's handbook *(1)* and Karel and Roach's dictionary *(2)*. The names are checked when information on the antibiotic can be found in these handbooks. The product and abstract file terms are checked when these sources contain information on the antibiotic. Both files are maintained by the library staff. The product file gives information on trademark and dosage form. The abstract file contains abstracts of articles of medical interest and thus constitutes a valuble source of clinical information.

Reproductions of the IBM card, punching code sheet, and master cards for puromycin are found in Figures 2 to 6.

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Method of Use

Many combinations of information may be obtained from this coding system. The specificity of information desired determines how many times the cards must be run through the electric sorter. For example, if the antibiotics active in vitro against gram-positive organisms only are desired, the gram-positive cards obtained will need a second run to search for gram negatives, mycobacteria, fungi, and parasites. The remaining cards will then be the gram positives only.

The user, of course, must modify his questions to suit the framework of the code —for example, the code has no category for antibiotics effective against plant bacterial diseases in vivo. However, because an article on this subject usually contains information on phytotoxicity, the user can find these antibiotics by searching for phytotoxicity and then for the bacterial group in which he is interested—e.g., nonindicative gram-negative if he is looking for *Xanthomonas*. This example also illustrates the principle of searching for the most specific property first, in order to reduce the number of cards obtained. If nonindicative gram negatives are searched for first, relatively few of the many cards obtained will contain information on phytotoxicity. The user who wants information on a specific antibiotic goes directly to the master card file, which is arranged alphabetically.

Discussion

The antibiotic literature file is most useful for chemical and limited biological data on little known antibiotics. Information on a well-known antibiotic, such as penicillin, may be found to better advantage in more complete sources. The primary emphasis of this file is chemical, but because chemical information is often not available, a limited basis for biological comparison is also provided. The file is useful also to answer questions concerning the names of new antibiotics and of antibiotic-producing *Streptomyces* species which have been described since the publication of Waksman's book *(3)*.

The user must be aware of the file's limited bibliography and the many important items it does not contain, such as clinical data, extraction procedures, and informa-

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

tion on synergism and resistance. Some of this information can be obtained by reading the references cited.

The file is obviously limited by the adequacy of the literature coverage, and in this respect it is subject to all the frailties of human literature searching. The fine facilities of the Lilly research library and the excellent cooperation of its staff have been of invaluable assistance in making the file as inclusive as possible.

Expansion of the scope of the file may become desirable. Inclusion of laboratory data is an example of a possible expansion. If each laboratory worker reported and coded the results of his own work, this would provide a much better basis of comparison of new with known antibiotics. However, the advantages of such expansion might not warrant the additional time and effort required.

This particular file could be organized in many different ways. If master cards were not wanted, a more complex code could be worked out, so that the literature references for the various groups punched could be coded directly on the IBM card. Edge-punched cards, with appropriate coding, could be used as master cards.

The file described is an example of an approach to literature coverage which may be equally useful in other fields of pharmaceutical and medicinal literature. Groups of substances that cannot be adequately described in terms of chemical structure lend themselves to this type of coding system. The field of plant products and, more specifically, of alkaloids is an example of such a group.

Suggestions for establishing a coded file are the usual ones. Work with the material long enough to become familiar with it before attempting to start a coding system. Keep the code as simple as possible. Allow room for expansion. If the file is to be used by other people, work with them in its organization in order to be sure it contains the information they want. Make a trial run before arranging the code in final form in order to be certain the information wanted can be extracted.

Acknowledgment

The author is indebted to M. H. McCormick and to R. C. Pittenger for assistance in establishing the coding outline, to Irene M. Strieby and the library staff for assistance in literature searching, and to Claudene Frank for assistance in organizing the code and IBM card arrangement.

Literature Cited

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Toxicology of Industrial Chemicals

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Important books, journals, and other sources of information on industrial toxicology are discussed, as well as test methods commonly reported in the literature, standards for expressing degree of toxicity, and some factors to be considered in evaluation of test results. The subject is approached from the point of view of the literature chemist rather than of the professional toxicologist, who usually makes the final decision on the test methods to be used in each particular case. Extensive laboratory experimentation is necessary to verify and supplement any available literature.

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The earlier writers in industrial toxicology were concerned with highly volatile substances such as solvents, with heavy metals such as lead, and with obviously poisonous gases. The books by Henderson *(17)*, Lehmann and Flury *(19)*, and Hamilton *(15)* are examples.

With the development of insecticides, food additives, and related applications of industrial chemicals, interest in toxicology has greatly increased. It has also come to be recognized that the toxicology of many chemicals may be of a more insidious nature than previously suspected. The field has become complex and now calls on the services of such specialists as physicians, biochemists, biologists, statisticians, and toxicologists. A complete test program for a single chemical may cost $20,000 or even more. Use of the currently available literature can save considerable time and effort in the planning, design, and interpretation of tests.

Current Journals

Industrial and Engineering Chemistry has a regular column on toxicology by H. H. Schrenk of the Industrial Hygiene Foundation at Pittsburgh. *The Industrial Hygiene Digest*, published by the Industrial Hygiene Foundation, is an excellent abstracting journal which covers the entire field. The *AMA Archives of Industrial Health* contains original research as well as abstracts from other journals. The *Current List of Medical Literature* published by the Armed Forces Medical Library and *Chemical Abstracts* are other sources of information on current journal articles.

Other journals of interest include: *Archives of Dermatology and Syphilology, Industrial Medicine and Surgery, Journal of the American Medical Association, Journal of the American Pharmaceutical Association, Journal of Pharmacology and Experimental Therapeutics, Journal of Tropical Medicine, Pharmacological Reviews,* and *Summary Tables of Biological Tests.*

For literature searches going back into the early literature, the literature chemist can use standard sources such as *Chemical Abstracts, Quarterly Cumulative Index Medicus, Current List of Medical Literature,* and the *Index-Catalogue of the Surgeon General's Library.* The U. S. Public Health Service has just issued a valuable index of selected toxicological literature for 1909 to 1953 *(26)*.

Books

In certain fields, there is a quantity of toxicological book literature. As would be expected, the literature on the toxicity of solvents is extensive. A recent book by Browning *(6)* provides an excellent summary covering also many chemicals not thought of primarily as solvents.

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Toxicity literature on pesticides is also extensive. For guides to, and summaries of, available information the following books are particularly recommended: Brown *(5)*; "Official Publication," Association of Economic Poisons Control Officials *(2)*; Barnes *(3)*; and Martin *(21)*.

Sollmann *(24)*, although he deals mainly with pharmaceuticals, has numerous references to the toxicology of chemicals which are also used in industry. Von Oettingen's recent book *(27)* presents a discussion of medical techniques for the management of industrial and other kinds of poisoning. This is information not easily located in other sources.

Hamilton and Hardy *(16)* have written an excellent up-to-date book on the toxicology of heavy metals and other substances which have long been of toxicological interest. Other recent authors of books of a more general nature include Elkins *(12)*, Sax *(23)*, Fairhall *(13)*, Patty *(22)*, and Jacobs *(18)*.

Other Sources of Information

Data sheets on the toxicology and safe handling of individual chemicals are published by the National Safety Council, American Petroleum Institute, and the Manufacturing Chemists' Association.

A recent publication of the state of California *(7)* is the best summary of available information on the toxic effects of chemicals on fish and other water life. Tests with aquatic life are, of course, not ordinarily related to the probable effects on humans.

Numerous toxicity studies have been conducted with chemicals used by the Armed Services, such as rocket propellants. Much of this research is summarized in reports issued from the Army Chemical Center and is frequently made available to the general public. Toxicity information as it relates to shipping is presented in the regulations of the Interstate Commerce Commission *(8)*.

The "Air Pollution Abatement Manual" issued by the Manufacturing Chemists' Association offers the most reliable information on this aspect of toxicology.

For any specific chemical, the trade catalog of the manufacturer will usually contain some toxicity information.

In the event that the information desired is not in the published literature, the literature chemist has access to such specialized sources of information as the Manufacturing Chemists' Association, the U. S. Public Health Service, the National Safety Council, the Industrial Hygiene Foundation, and the Chemical-Biological Coordination Center of the National Research Council. Many trade and professional associations have toxicity committees which can supply additional information.

The prediction of the probable toxicity of a chemical by reference to the known toxicity of a compound of similar structure is a complex and risky business best left to specialists in this aspect of toxicity. Toxicity can vary more unpredictably and more sharply than physical properties even in a closely related series of compounds. However, some general guides will be found in the introduction to Fairhall's book *(13)* and in Patty's book *(22)*.

Toxicity Test Methods Commonly Used in the Literature

In order to interpret properly toxicity data reported in the literature, it is necessary to understand the fundamentals of the various test methods. Some of the most important methods are described here as they are commonly used in the literature. The comments here are mere description and not recommendations to practice. The actual choice of the test method to be used in any particular case should be made by a professional toxicologist.

Tests are described as acute, subacute, or chronic depending on the nature and duration of the test. Test methods include oral ingestion, inhalation, skin penetration, skin irritation, sensitization, and intravenous and intraperitoneal injection. While all test methods may be used, emphasis is usually placed on the test or tests relevant to the method of manufacture, the intended end use, and the probable routes of entry into the human system.

Oral Administration. Data on toxicity by oral administration are most frequently available in the literature. This is usually the first phase of testing, which is done to establish the relative toxicity of the chemical. Administration may be by stomach tube or by addition to the animal's food and water. Naturally, the former

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route brings quicker results. Toxicity is designated as LD_{50}, which means the lethal dose to 50% of the test animals; this is reported in milligrams per kilogram of body weight. The LD_{50} is a figure chosen arbitrarily because it is the median or average figure. When toxicities were originally reported, the "toxic point" was chosen to be the dosage at which no animals died (LD_0). This was later changed to the dosage which killed all the animals (LD_{100}). To arrive at a figure with a minimum factor of error and a figure that would hold individual variations to a minimum, the LD_{50} was adopted. The proposal of this standard in 1927 brought a considerable impetus to research on toxicity *(4)*.

The animals most frequently used are rats and mice. Rats are cheap, fertile, healthy, and standardized, but it is much less expensive to use mice; initial cost and the caretaking cost are less. They are, however, more difficult to handle because of their small size. The degree of sensitivity or response to a chemical naturally varies with the animal. An accurate picture can be obtained by using two or three species—for example, the toxicologist may do preliminary work with rats, then dogs, and finally monkeys.

The selection of the number and kind of animals to be used requires considerable skill. Typically, the animals selected for testing are young, healthy, and paired for ascertaining sex differences.

The material is usually administered to animals which have been without food for 24 hours and it is best given as an aqueous or edible oil solution or suspension. This is not always possible, so alcohol as a solvent is permissible if it does not exceed 25% (15% is preferable). The animals ordinarily have adequate living quarters such as individual cages, air conditioning, and proper food and water. First the LD_0 and LD_{100} dosages are determined. Next a minimum of four groups of animals consisting of a minimum of five animals each, and preferably ten, should receive single doses varying between the LD_0 and LD_{100}. More than ten animals in the group does not add significantly to the accuracy of the determination, as most physiological reactions have a 10% deviation in accuracy. After the animals have received their dosage, they are observed for one week. Animals that die are examined for gross pathology. The results are tabulated and plotted on semilogarithmic paper, with the per cent mortality on the abscissa and the dosage in milligrams per kilogram of body weight on the ordinate (logarithmic scale so that a relatively straight line is obtained). The dose killing 50% of the animals is the LD_{50} of the compound.

The National Safety Council uses the following table as a guide in extrapolating animal data to humans *(9)*.

Rating	Dosage Range of LD_{50} (Corrected by safety factor)	Probable Lethal Dose for 70-Kg. Man
Dangerously toxic	1 mg. or less/kg.	A taste
Seriously toxic	1 to 50 mg./kg.	A teaspoonful or 4 ml.
Highly toxic	50 to 500 mg./kg.	An ounce, 28 grams
Moderately toxic	0.5 to 5 g./kg.	A pint
Slightly toxic	5 to 15 g./kg.	A quart
Extremely low acute toxicity	15 g. and upward	More than a quart

"Range finding" LD_{50}, while less accurate than the method described above, is helpful in estimating the relative toxicity of a chemical. Groups of five rats receive three or four dosage levels in a series differing by a factor of two. The range finding LD_{50} is then calculated.

The comparative reliability of the approximate lethal dose and the method of maximum likelihood are discussed in a paper by Diechmann *(10)*.

Inhalation. If the means of poisoning by industrial chemicals is to be considered in importance, toxicity by inhalation would be foremost. This is the easiest and most dangerous type of poisoning. It can be rapid, severe, and acute, whereas oral poisoning is usually slow, mild, and sometimes chronic. Fumes from liquids, and dusts from solids and gases can enter the lungs and be absorbed quickly into the blood stream. Control of contamination of the air is difficult. Dust, fumes, and gas continually escape into the air when chemicals are being manufactured and used.

Inhalation toxicity may be in the form of irritation, asphyxiation, damage to central and peripheral nerve centers, or destruction of the elements of the blood. Many of the common industrial chemicals when present in the air in high concen-

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trations will cause one or more symptoms. The majority of the well-known industrial chemicals have been thoroughly enough investigated to provide adequate safety measures. Threshold limit values have been established for many industrial chemicals by the Committee on Threshold Limits of the United States Public Health Service. Values established by this committee are designed to protect the health and comfort of the worker. Values that would not necessarily impair the health but do cause discomfort of the worker are sometimes reduced to a figure that will give freedom from irritation. Foulger in a recent publication *(14)* and others caution that threshold limits can be taken only as a very general guide. Such limits are not precise scientific figures, owing to shortcomings of analytical methods and differences in working conditions and individual respiratory rates.

In a recent publication of the Bureau of Mines *(25)*, the 1953 threshold limit values are given together with the variations adopted by the various states; 1955 values are also now available *(1)* for some 165 compounds. The threshold limit value is usually expressed as MAC or maximum allowable concentration (for an 8-hour working day) in terms of parts per million. Annual revisions of these values seem to be following a trend to more conservative or lower values as human experiences increase.

The Committee on Threshold Limits bases its values on data accumulated from animal inhalation toxicity studies and industrial experience. A safety factor of 10 is used to allow for differences in response between man and animal. When industrial experience is not available, animal data and the experience of occupational hygienists must be used in order to ensure protection of the workers. If data are relatively scarce, a larger safety factor is used and this can be as high as 100, depending upon the possibility of engineering control and on analytical methods sensitive enough to determine the amount of the chemical present.

Toxicity testing on inhalation can follow the minimum standards as outlined by the National Safety Council. Six rats of Sherman strain, male albino, 90 to 120 grams in weight, 5 to 6 weeks of age, are used. They are subjected to saturated vapor at room temperature. If two, three, or four of the six die after 5 minutes, the hazard is serious; if two, three, or four die after 15, 30, or 60 minutes, the hazard is definite; if two, three, or four die after 2 to 4 hours, moderate; and after 8 hours, slight. Compounds which are more toxic than "slight" are given additional study.

Skin Penetration. Acute skin penetration can be determined accurately by following the method as outlined by Draize *(11)*, which involves using a sleeve to hold the chemical in place on the bared skin of groups of rabbits.

Skin Irritation. Skin irritation studies are done by using extremely sensitive skin on the belly of albino rabbits. A method has also been outlined by Draize *(11)*.

Sensitization. Sensitization work is more complicated. The animals, usually guinea pigs, are injected intracutaneously every other day until a total of ten injections have been given. Two weeks after the last sensitizing injection another injection is given and the animals are observed for reactions. Tests on human subjects are sometimes done.

Eye Irritation. For eye irritation studies the rabbit is used. The chemical, undiluted or diluted in a harmless vehicle, is introduced into the rabbit's eye. It is examined then and again after 24 hours. Damage is determined and the chemical is scored.

Injection. Intraperitoneal and intravenous administration are important in drug work, but accidental entry by these routes is improbable in an industrial situation. Intraperitoneal studies are valuable in studying manifestations of toxicity where relatively slow absorption is desirable or permissible.

Acute toxicity tests usually are designed to get quick positive or negative results as evidenced by death. **Subacute tests** are 2- to 4-month tests, during which time there is more opportunity to study such factors as metabolism, growth rate, blood, and fertility. **Chronic toxicity tests** usually extend for 1 to 2 years and are designed to show up unfavorable effects which might not appear in the shorter tests and are used particularly with proposed food additives.

Interpreting Toxicity Test Results

The complexities of the proper extrapolation of toxicity test results to man are well presented by Barnes *(4)*. He urges that more attention be paid to the sub-

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acute tests and in particular to biochemical studies of the effect on metabolism. Other factors and tests are relatively less meaningful.

It is impossible to predict the exact reaction in man from animal data. Nevertheless, the majority of substances which are toxic to rodents are toxic to man, and vice versa. Furthermore, small animal testing does give indication as to the type of toxic action which the chemical produces. A safety factor of at least 10 is applied to animal test results, as man is considered more sensitive to chemicals. For chemicals to be used in foods or where some experimental data are lacking, safety factors up to 100 may be used.

In addition to criteria developed by the Committee on Threshold Limits of the U. S. Public Health Service and by the National Safety Council, other criteria for rating toxicity have been developed by the Interstate Commerce Commission in Campbell's Tariff *(8)*; by the Underwriter's Laboratories; and in regulations issued under the Federal Insecticide, Fungicide, and Rodenticide Act *(14)*. Fairhall *(13)*, Foulger *(14)*, and "Guide to Safety in the Chemical Laboratory" *(20)* give good general discussions on the value and interpretation of toxicity tests.

Conclusions

In looking at any article describing data on toxicity, the following are some criteria to be considered.

How was the chemical administered? Toxicity of a chemical may vary, depending on the route of administration and the number and kind of test animals.

Was the test for acute or chronic toxicity? Very often a chemical may not be toxic on an initial dose, but may have accumulative chronic effects when testing is conducted over a long period of time.

What solvent was used in the test? In the case of oral ingestion the use of excessive quantities of a solvent which is itself toxic may affect the final results.

Was a pure or commercial product used? The commercial grade of a chemical will often contain impurities which will affect the final result. Toxicity may vary from batch to batch. Thus, the use of a pure chemical in the test does not have the value it usually has in physical and chemical testing. The test should be run on the product as it will be manufactured or sold in commerce.

What are the other basic properties of the chemical? Its vapor pressure, odor threshold, and solubility may all affect the final results. Volatile substances are usually more of a hazard, everything else being equal. A compound with a high odor threshold may give adequate warning before the safe limit is passed. Solubility in body water and fats may be so high that absorption through the skin may be particularly dangerous.

Acknowledgment

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Literature Searches for Uses of New Botanical Drugs

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About 900 plant species are used in the American drug trade. Many officially recognized drugs of plant origin have resulted from exploration of remedies that formed the basis of ancient folklore, and traditional remedies and country cures may eventually prove to have a basis in fact. The literature sources referring to medicinal drugs suffer by comparison with the well organized compendia of chemistry and other scientific fields associated with medicine. Over 500 periodicals deal with pharmacognosy alone. Diversity in botanical character, geographic origin, and medical use makes difficult the systematic classification of plant drugs and plant sources of drugs, and complicates the search for new botanical drugs.

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Perhaps an illuminating subtitle for this discussion would be: "How to Find Another *Rauwolfia.*"

It may be well to review the process by which *Rauwolfia* came to be of such interest in recent months, when it is a drug that has been known and used in India for years. The roots of the plant *Rauwolfia serpentina* have been recognized in India as a medicine from ancient times. Its alleged therapeutic effects varied from antidotal properties against bites of poisonous reptiles and stings of insects, to a cure for dysentery, and as a febrifuge and abortifacient.

For years research workers in India have been systematically reviewing their Materia Medica—the drugs used for so long by Indian physicians. It was a well organized approach; the details are well documented in the many excellent papers published on *Rauwolfia.*

Where did they start? To answer that question would require certain knowledge of the genesis of the ideas in the minds of those workers, ideas of where to look and what to investigate.

They did look in their own back yards. The flora of the Indian peninsula is rich, as one might expect in a country two thirds the size of the United States, with a variety of climates, soils, and latitudes. Kashmir in the north is not unlike Switzerland, and the Malabar Coast is like the coast of proverbial South Sea Isles. Between lies the Sind Desert, not unlike the Sahara, and in the jungles of Assam some of the heaviest rainfalls in the world occur.

Rauwolfia is mentioned in the Charak (1000 to 800 B.C.), one of the old books of Hindu medicine. As long ago as 1690 it was used in Europe, and the "Herbarium Alboineuse" of 1741 states that "it is invaluable in anxiety states." It is also said that the late Mahatma Ghandi drank *Rauwolfia serpentina* tea nightly because of its calming effect.

In later years the drug attained prominence as a remedy for insomnia, hypochondria, and insanity. Its hypnotic and sedative action is not mentioned in the ancient writings, although the drug appears to have been known for some time to the poorer classes in Bihar, in Northern India, who made use of the hypnotic properties of this drug in putting children to sleep.

The drug is now official in the British Pharmacopoeial Codex and the Indian Pharmacopoeial list.

The first mention of its possible use in treating high blood pressure was in India

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in 1931, and the earliest published report of American clinical work appeared in February 1952.

Difficulties of Search for Drugs

Some sources—for example, the "Pharmacographica Indica"—have to do specifically with Indian medicinal plants; other references, such as Hooker's "Flora of British India," are more general in their scope. But there seldom are clear signposts which point to possible modern uses of these drugs, and sometimes the modern use is not too closely related. One difficulty lies in the paucity of accurate information available as to the former use of the drugs.

Another difficulty lies in indefinite or inaccurate descriptions or diagnosis of diseases. For example, if cancer did exist 1000 years ago, how was it diagnosed? What type of cancer was it, or was the tumor nonmalignant? In the instances of reported cures for syphilis, was the primary case cured or was the secondary stage unrecognized—and the tertiary subsequently called another different disease?

These examples are but a few of the many which could be mentioned. Very few ancient remedies were listed as specifics. Most had multitudinous uses, and most concoctions and prescriptions were of the "shotgun" type.

The sources of information about new botanical drug uses, unfortunately, have no general category of title.

Books have been published covering the flora of most civilized and many uncivilized areas—for example, there is a "Flora of the Eastern United States and Canada," of the Eastern United States, of New York State, of New York City, and of Staten Island. Each serves some function and has a definite value. Some are nicely annotated, such as the "Flora of West Tropical Africa" written by Hutchinson and Dalziel *(14)* and currently being received and brought up to date by a team of botanists working at Kew Gardens, near London. These annotations frequently refer to the medicinal or poisonous character of the plants, or to their economic value as food or timber.

Poisons

But most such publications give no information as to the usefulness of the plants. So we come to references which contain the words "Useful Plants" in their titles—or words of similar connotation, such as "Useful Plants of the World" by Chute *(5)*, or "Plantas Usual de Venezuela" by Pittier *(21)*. While the word "useful" is a clue, so is the word "poisonous." Most drugs are poisons, though most poisons are not suitable for use as drugs. Two references by way of example are "Poisonous Plants of New South Wales" *(13)* and "Stock Poisoning Plants of the Range" *(32)*.

Many modern drugs had their first use as poisons—*Strophanthus* and curare for hunting wild animals; *Physostigma* beans in tribal ordeals; *Oleander*, a famous medieval poison of the Borgias. And there are many other examples.

These poisonous plants could lead us to review and then to expand our knowledge of the families of poisonous plants.

However, not all families of plants fall into recognizable, popularly known categories. There are exceptions: The *Cruciferae* or mustard family are noted weeds. The *Salicaceae* or willow family provide many beautiful shade trees. The *Solonaceae* or nightshades are rich in poisonous, and frequently medicinally useful, alkaloids. The *Dioscoreaceae* or yams are rich in steroids. The *Apocynaceae* are noted for their latexes and poisonous glycosides.

Such characteristics as these might suggest a starting point for seeking plants of potential medicinal value. The plan would be based on a systematic review of certain carefully selected plant families.

More than one attempt has been made to classify plants, particularly drug plants, on an artificial basis.

The matter of morphology—leading to a study of barks or leaves or roots, as a group—is not particularly rewarding. It is little more than a tool for identification.

The systematizing of plants on the basis of their constituents is a relatively new approach to pharmacognosy but an old interest of plant chemists. Many related plants do have related constituents. Take the *Solonaceae* family as an example. Most poisonous solonaceous drugs share many alkaloids in common—scopolamine,

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for example. But there are cases which point up the falsity of such relationships. For example, anethol is a constituent of anise oil from *Illieium verum* of the magnolia family and of *Pimpinella anisum* of the *Umbelliferae* or parsley family, two very widely separated families. Caffeine is found in coffee of the *Rubiaceae*, in tea of the *Theaceae*, and in Kola of the *Sterculiaceae*—three quite unrelated families.

These occurrences of the same or related constituents in different plants or plant families can frequently be put to good use. Rutin is a good example.

The original source for commercial supplies of rutin was buckwheat, *Fagopyrun esculentum*. The yields were not too good. The product was not entirely satisfactory and the crude was expensive. A literature search for all possible sources of rutin soon suggested that the flower buds of *Sophora japonica* might be a good source. This proved to be very happily correct.

Rutin takes its name from rue, an herb of the *Rutaceae*. Yet the first commercial supplies came from buckwheat of the *Polygonaceae* and the eventual commercial source was *Sophora* of the *Leguminosae*. These three families of plants are quite unrelated, botanically speaking.

Today much is known about many of the genera and species of plants and some 2000 new species of plants are being discovered every year. Most of these new plants are reported from the still uncivilized areas of the world, such as the Central Amazon basin, the lesser known (botanically) islands of the Pacific, such as New Guinea, and the far reaches of Siberia and Mongolia.

To extract, analyze, test, and evaluate all these potential materials is more than a lifetime's work for many men.

To look for medicinal plants as such—plants usable in whole or extract form—is far from the end result desired. Many plants yet to be named and tested can be expected to yield chemicals as yet unknown and active principles which could be modified to creat new medicinal substances.

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Alkaloids

Consider the groups of alkaloids, about which little is known. Yohimbine and certain *Rauwolfia* alkaloids are related, and not at all well understood. These two, and their related alkaloids, are by no means the only examples of the fields where our knowledge is lacking.

Considering the number of known valuable medicinal plants and their derivatives, and the number of still-to-be-discovered plants and active principles, the surface has been well scratched and picked over, but the fertile field remains to be tilled.

There may still be much to be learned from ancient medicine. Psychosomatics is a relatively new science. Mental diseases having organic or structural relationships, and the medicaments of possible use in these sciences are just beginning to be reviewed, considered, and investigated.

Mescal or Peyote produces hallucinations in technicolor. Here is a tool at least for investigational purposes. Certain steroids have a definite relation to fatigue. Fatigue borders on mental breakdown and neuroses. A number of medicinals have been used in former days in the treatment of mental illness—*Rauwolfia*, valerian, sumbul, lupulin, and viburnum. Is it not reasonable to inquire into the mechanisms by which some of these drugs act, especially now that certain of them have proved to be of value?

Anthropology and Theology

To return closer to the subject, there are other branches of science and the arts which might give valuable leads—for example, anthropology and theology.

As for anthropology, here we could study primitive tribes and their practices. Previously mentioned were primitive ordeals, tribal customs, and the drugs of the medicine man.

Perhaps typical of the reviews of folk medicine was the work done by Natalia Ossadtscha-Janta on folk medicine of the Ukraine. A translation of her work was sponsored by the New York Botanical Garden. The original research was conducted among the peasants. Her work has not yet been evaluated. Possibly there are many valuable leads contained in her thesis; the only difficulty would be in obtaining samples of the drugs from Russia for study.

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Again in recent years, some attention has been focused on Egypt. This serves to remind us of the findings made when the Ebers papyrus was deciphered and published. In this ancient document reference was made to certain diseases such as cardiac ailments and many drugs, including Styrax and castor oil. This one example serves to show us how far back we may look.

In our own country some knowledge of herbs was taken from the Indians. A fine book on this topic was written by the late G. L. Wittrock *(35)*.

Another source of much knowledge and wisdom is the Bible. Probably the best and most recent work on the drug plants and other plants of the Bible is that of Moldenke *(18)*.

Theology leads to interesting studies. In this regard missionaries should not be overlooked. Many are fully qualified physicians; if an example is required, none better than Albert Schweitzer need be mentioned. Missionaries come to know their people and are trusted.

Early References to Medicinals

One of the earliest references to ipecac was by Samuel Purchas in his "Pilgrimes" *(23)*. Purchas wrote rather extensive accounts of his travels, but his descriptions of the drug and its uses were not too lucid. He said ipecac was used for the "bloudie fluxe." More definite information about ipecac is given by Guilelonus Piso in "Historia Naturalis Brisliae," published in Amsterdam in 1648, As an indication of how interest grew—the first quantities of ipecac went to Europe in 1672.

Opium is such an ancient drug that its early beginnings are not definitely known, but it was used as early as the third century B.C. and was described by Theophrastus in 1483 *(31)*.

As for aloes, there are references to this popular laxative by Dioscorides in 1518 *(6)* and by Claudius Galen in 1525 *(7)*.

Most of these works are on early general science, natural sciences, or explorations. It is doubtful if all such works have ever been thoroughly reviewed in recent years. It would be a monumental task to review even a section of them. All the same, they are occasionally very useful.

Recent Publications

Probably one of the most fertile fields for these literature searches is recent publications. A list of "Serials Pertaining to Pharmacognosy and Pharmacology" was prepared by George M. Hocking in 1944, when he was chief pharmacognosist of S. B. Penick & Co. The serials pertaining to pharmacognosy then numbered over 500. Since that time some new publications have appeared, such as *Economic Botany*, and some have disappeared. Most of the changes have taken place in foreign publications.

From a regular reading of these journals a number of ideas can be gleaned. Frequently the original idea is to be taken from a list of plants studied for some particular aspect, such as the work being carried on in Australia. A research team is systematically collecting all possible Australian plants and testing them for cardiac glycosides. Work is being done by the United States Department of Agriculture, Eastern Regional Research Laboratories, in Philadelphia to screen plants for steroids. Much more work of this type could be done, probably to advantage, provided the objectives were both reasonably and clearly defined to avoid a wild-goose chase. The difficulties of delineating an intelligently planned program are many, but the work to be done is none the less important and it holds reasonable promise of reward.

The chemical literature is particularly helpful as a source of leads when the problem is to isolate, identify, and correlate active plant principles. A wealth of information can be gleaned from *Beilstein*, *Chemical Abstracts*, and *Biological Abstracts*. Another standard reference on the chemical constituents of many plants is Klein's "Handbuch der Pflanzen Analysen," and specialized works are Henry's "Alkaloids" and the "Glucosides" by Armstrong.

To uncover these valuable plant constituents requires the concerted efforts of the botanist, the chemist, the microbiologist, the pharmacologist, and the clinician.

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In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
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Therefore, to obtain an idea of the usefulness of a plant or of its constituents, a careful watch of a wide variety of scientific literature is necessary.

Starting a Literature Search

A literature search for new botanical drug uses could be commenced from one of several points.

There is that fund of knowledge to be investigated in related but sometimes somewhat remote publishings, such as annotated floras, reports of expeditions, books on economic botany, and accounts of ancient tribal customs. There the object would be to find plants having some reported use or action, which suggests usefulness to modern medical practice.

A second starting point would be a systematic investigation of certain groups of plants having a natural or geographic or artificially chosen relationship.

Finally there are many recent publications on experimental pharmacology. Here the lead is taken from the reported action of the drug itself. The problem then is to find a reliable source of the specific drug, or to locate supplies of an allied drug having the same or similar constituents. Such searches are in the province of pharmacognosy and its many ramifications.

These particular literature searches present many unique problems, especially when the literature is not as well organized as it is for law, chemistry, or physics.

The diversity of works cited here amplifies the magnitude of the problem. The references cited are by no means meant to be exhaustive. If the list were inclusive, even to a modest degree, it should include almost every book ever published on economic botany, exploration, plant chemistry and pharmacology, and hundreds of other fields as well.

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Pyrogens

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Pyrogens, which may contaminate improperly prepared drugs and cause fever on injection, are formed by certain microorganisms as they grow. These febrile agents are among the most physiologically active substances known, as even submicrogram quantities can cause pronounced fever and blood and adrenal changes as well as other effects. The isolation and chemistry of purified pyrogens, the methods used in their prevention, removal, and destruction, and physical, chemical, and biologic test methods are reviewed. An extensive bibliography on biologic and clinical studies is included.

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Parenteral administration of improperly prepared sterile nutrients or medicaments sometimes produces a febrile response in man and in certain other animals. The agents causing this reaction, which are known as "pyrogens," have been shown to be metabolic products of microorganisms. Whenever pharmaceuticals are to be injected, these thermogenic agents pose an important medical problem.

Pyrogen-producing bacteria are ubiquitous; many are air-borne and require only trace amounts of essential elements for growth.

Most of these fever-producing substances are active even in submicrogram quantities; therefore, relatively little bacterial contamination may be sufficient to render a drug pyrogenic.

Although ordinary steam sterilization destroys pyrogen-producing bacteria, pyrogens are relatively heat-stable and not notably affected by sterilization.

The constancy of this problem and its importance in medicine have led to a miscellany of publications; in all, over a thousand papers *(300)* dealing with pyrogens have appeared. The excellent review of Bennett and Beeson *(59)* emphasizes particularly the physiological and medical problems associated with pyrogens. This paper deals mainly with the following aspects of the field:

Isolation and chemistry of purified pyrogens.
Prevention, removal, and destruction of pyrogens.
Physical, chemical, and biological test methods.

The fact that ordinary distilled water can produce a febrile response when administered intravenously has been known since 1865, when it was reported by Billroth *(78)*. In 1876, Burdon-Sanderson *(108)* first used the term "pyrogen" to refer to a fever-producing substance which he isolated from putrid meat. These and other investigators *(69, 107, 280, 567, 625)* noted many examples of injection fever. By the early part of the twentieth century, such misnomers as "protein fever" *(747)*, "salt fever" *(109, 110, 704)*, and "Salvarsan fever" *(704)* had come into use. A number of papers appeared in 1911–12 contributing to the evidence that such terms were improper and that actually bacterial contamination was responsible for the pyrogenic activity of many parenterals.

During this period, Wechselmann *(769, 770)* showed that Salvarsan fever was caused by bacteria in the water used in preparing the solutions, Bendix and Bergmann *(53)* and Samelson *(631)* noted that contamination was the cause of salt fever, and Muller *(520)* obtained bacterial counts on several samples of distilled water. In a series of carefully controlled experiments, Hort and Penfold *(374–380)* proved that bacterial contamination of water was the basic cause of injection fevers.

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They also showed that solutions may be free of microorganisms but still be pyrogenic, and that "the contaminating principle in such water or saline . . . is a heat-stable . . . molecule incapable of removal by ordinary methods of filtration" *(376)*.

These investigations and other confirmatory reports *(427, 518, 519, 572, 611)* were apparently ignored by many workers *(27, 111, 150, 613, 745)* in the field until the classic work of Seibert and coworkers *(93, 652–657)* first reported in 1923. The latter investigators carefully eliminated other possible factors one by one and proved conclusively that all of the injection fevers had a common etiology—a microbiological source. Seibert isolated pyrogenic organisms from contaminated solutions, showed stability of the pyrogen to heat, and first suggested the use of the rabbit as an assay animal for its detection.

Isolation and Chemistry

The earliest reported work on the isolation of a fever-producing substance from bacteria was that of Roussy *(624)* in 1889, who separated crude pyrogens from gram-negative organisms. This was closely followed by the work of Kanthack *(411)*, who demonstrated the presence of fever-producing substances in several microbial species. Several years later, Centanni *(125, 126)*, working with bacterial cells, isolated an improved pyrexic product by water extraction, alcohol precipitation, and dialysis. It was Centanni who first demonstrated the nonprotein nature of pyrogens. In the early part of the twentieth century, other workers *(543, 651)* reported the isolation of fever-producing substances. In 1915, Jona *(408)* described the preparation of nonprotein, heat-stable, thermogenic substances from both *B. coli communis* and *E. typhosa*. Injection of these materials into rabbits in 4γ quantities elicited a febrile response of 3° F.

These and other studies on bacterial pyrogens, many of which closely paralleled isolation studies on vaccines, antigens *(79, 251, 510, 511)*, and toxins have provided important data concerning these fever-producers. The early and recent work shows that, regardless of source, pyrogens have similar physical properties. They are filterable, macromolecular solids, dispersable in water, and insoluble in the common organic solvents. Molecular weights have been reported ranging from a low of 15,000 to a high of 4,000,000 *(481, 616, 645, 782)*.

Sources and Isolation Procedures. Within the past several years, a number of investigators have separated highly purified pyrogens of a polysaccharide nature from bacterial sources—either cells or culture broths. In either case, the pyrogen represents but a small portion of the total starting material, and isolation procedures entail the removal of growth media and cellular debris, including such extraneous constituents as proteins, peptides, amino acids, nucleic acids, unbound lipide, and salts. Various procedures have been employed for the removal of these nonessential components, leading to highly pyrogenic preparations. Table I lists some of the techniques that have been employed in their isolation and the major nonessential constituents removed. The preparation of "pure pyrogens" always involves the use of a combination of these procedures.

Table I. Procedures Used in Isolation of Pyrogens

Technique	*Constituents Removed*	*Reference*
a. Mechanical cell rupture		*(512, 774)*
b. Salt-alcohol fractionation	Protein, nucleic acid, unbound lipide	*(392, 510, 512, 566, 668)*
c. Alcohol fractionation	Protein, nucleic acid, unbound lipide	*(351, 392, 512, 566, 668, 724, 772, 786, 787)*
d. Acetone fractionation	Protein, nucleic acid, unbound lipide	*(192, 724, 772, 774)*
e. Trichloroacetic acid precipitation	Protein, nucleic acid	*(392)*
f. Acetic acid precipitation	Protein, nucleic acid	*(192, 616)*
g. 88–95% phenol extraction	Protein, nucleic acid	*(166, 192, 566, 618, 724)*
h. 50% phenol extraction	Protein, nucleic acid	*(772, 786, 787)*
i. Diethylene glycol extraction	Protein, nucleic acid	*(79)*
j. Tryptic digestion	Protein	*(299, 351, 535, 724)*
k. Dialysis	Amino acids, peptides, salts, low mol. wt. substances	*(166, 299, 351, 392, 535, 618, 668, 724)*
l. Sevag deproteinization	Protein	*(618, 724)*
m. Ultracentrifugation	Nucleic acids	*(787)*

Table II records various organisms from which pyrogens have been isolated, the process used in their isolation, and certain analytical data. The letters used in

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Table II to indicate the process employed correspond to the letters employed in Table I under "Technique." As highly purified pyrogens have been shown to be largely polysaccharide in composition, increasing reducing sugar and decreasing nitrogen values serve as criteria for evaluating comparative purity of preparations from a single species. It is thus possible to compare the effectiveness of various techniques as applied to a specific organism.

Table II. Pyrogens Isolated from Various Organisms

Microbial Source	*Process*[a]	*N, %*	*Reducing Sugar, %*	*Reference*
Studied by several investigators				
B. subtilis	d, k, l, g	1.4	56.0	*(618)*
	j, k	4.4	23.9	*(299)*
E. coli	j, k	7.6	9.3	*(299)*
	c, k, e	1.7	63–65	*(392)*
	h, c, m	0.97	76.0	*(787)*
E. typhosa	b, c, k, l	—	—	*(510)*
	b, c, k, l	7.0	13.4	*(512)*
	g, b, c	3.4	—	*(566)*
	b, g, c, k	1.5	30.0	*(166)*
	d, f, k, g	0[c]	—	*(616)*
	d, k, l, g	2.9	46.0[b]	*(618)*
	j, k	6.7	5.1	*(299)*
Proteus vulgaris	d, f, k, g	0[c]	—	*(616)*
	d, f	—	—	*(190)*
	j, k	8.0	9.6	*(299)*
Pseudomonas aeruginosa	c, k	—	—	*(125, 126)*
	a	—	—	*(774)*
	d, f, k, g	0[c]	—	*(616)*
	d, k, l, g	8.0	40.8[b]	*(618)*
	j, k	6.93	14.2	*(535)*
S. marcescens	b, c, k, l	3.84	—	*(668)*
	b, c, k, j	2.0	64.0	*(351)*
	d, k, l, g	0.7	68.0	*(618)*
	j, k	7.0	11.9	*(299)*
	c, g, j, k	—	—	*(724)*
Shigella paradysenteriae	d, k, i	6.79	35.5	*(79)*
	h, c	—	—	*(786)*
Studied by one investigator				
B. ent. breslau	h, c	1.4–1.6	65–70	*(786)*
B. fluorescens	h, c	2.5–3.5	—	*(786)*
Diplococcus pneumoniae	c, k	—	—	*(125, 126)*
Erysipelococci	c, k	—	—	*(125, 126)*
Lact. aerogenes	h, c	2.3	—	*(786)*
S. abortus equi	h, c	1.5–2.0	55–60	*(786)*
Staphylococci	c, k	—	—	*(125, 126)*

[a] See Table I.
[b] Part of reducing sugar due to nucleic acids.
[c] Nitrogen by sodium fusion.

Table III lists some of the bacteria, molds, and viruses, and a yeast which have been found to be pyrogen producers. These organisms were not fractionated, but killed suspensions or filtrates were tested for the presence of pyrogens.

Chemical Composition. Several purified pyrogens together with the pertinent analytical data concerning them are presented in Table IV. Inspection of the table indicates that pyrogens are primarily polysaccharides, since after hydrolysis the amount of reducing sugar expressed as glucose ranges from 55 to 76%. The polysaccharide portion is a complex one, as paper chromatography has shown the presence of three or more sugars in the hydrolyzates from each pyrogen. Glucosamine and possibly glucose are common to all of the preparations, but certain other sugars seem to be present in some pyrogens but not others.

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Table III. Some Pyrogen-Producing Organisms

Microbial Source	*Reference*
Bacteria[a]	
Gram-negative organisms	
Achromobacter candicans	*(169)*
Achromobacter lacticum	*(169)*
Achromobacter pinnatum	*(169)*
Achromobacter punctatum	*(169)*
Achromobacter refractans	*(169)*
Achromobacter solitarium	*(169)*
Achromobacter tiogense	*(169)*
Achromobacter W 14 B	*(169)*
Achromobacter W 14 C	*(169)*
Achromobacter 2 W S	*(169)*
Aerobacter cloacae	*(590)*
E. formica	*(169)*
E. freundii	*(590)*
Neisseria intracellularis	*(169)*
Pseudomonas ovalis	*(590)*
Pseudomonas scissa	*(169)*
Pseudomonas ureae	*(169)*
Proteus morgani	*(814)*
S. kilenes	*(814)*
Vibrio comma	*(169)*
Vibrio metchnikovi	*(411)*
Gram-positive bacilli	
B. cereus	*(590)*
B. mycoides	*(814)*
B. tumescens	*(590)*
Diphtheroids	*(590)*
M. tetragena	*(814)*
Gram-positive cocci	
Micrococcus candidus	*(590)*
Micrococcus epidermidis	*(590)*
M. flavus	*(590)*
M. subflavescens	*(590)*
Streptococcus equinus	*(590)*
S. faecalis	*(590)*
S. liquefaciens	*(590)*
S. pyrogenes	*(169)*
Staphylococcus aerogenes	*(590)*
S. albus	*(590)*
S. epidermidis	*(590)*
Molds	
Alternaria tenuis	*(342)*
Aspergillus Sp-A-1	*(429)*
Aspergillus flavus	*(342)*
Aspergillus niger	*(342)*
Aspergillus ochraceous	*(342)*
Aspergillus oryzae	*(342)*
Aspergillus versicolor	*(342)*
Blakeslea trispora	*(342)*
Cephalothecium roseum	*(342)*
Curvularia lunata	*(342)*
Fusarium (unknown species)	*(342)*
Fusarium roseum	*(342)*
Gliomastix convoluta	*(342)*
Gliocladium roseum	*(342)*
Penicillium (unknown species)	*(342)*
Stachybotrys atra	*(342)*
Torulopsis rosea berl.	*(429)*
Trichoderma viride	*(342)*
Viruses	
Enders-A	*(279)*
Influenza	*(65, 67, 753, 755)*
Lee-B	*(279)*
Mel. A	*(279)*
Swine influenza	*(279)*
Mump	*(753)*
Yeast	
Saccharomyces	*(411, 429)*

[a] Among the bacteria, the gram-negative organisms are the most pyrogenic, the gram-positive bacilli less pyrogenic, and the gram-positive cocci the least pyrogenic.

Table IV. Analysis and Activity of Several Purified Pyrogens

Bacterial Source	Reducing Sugars after Hydrolysis: % as glucose	Reducing Sugars after Hydrolysis: Sugars found	Lipide, %	Phosphorus %	Nitrogen, %	Minimum Pyrogenic Dose[a], γ/Kg.	References
S. marcescens, broth	65–70	Aldohexose, glucosamine, methylpentose	16	1.1	2.2	0.005	*(41, 352, 410, 668)*
S. marcescens, cells	68	Glucosamine and other sugars	—	0.4	0.7	0.005	*(618)*
E. coli, broth	63–65	Glucose, glucosamine, galactose	21–28	1.41	1.9	—	*(392)*
E. coli, cells	76	Glucose, glucosamine, galactose, rhamnose, xylose, desoxypentose	13	2.08	0.97	0.002	*(469, 783, 787)*
S. abortus equi, cells	55–60	Glucose, galactose, rhamnose, mannose, glucosamine, desoxypentose		3.1	1.5–2.0	—	*(786)*
Ent. breslau, cells	65–70		—	2.2	1.4–1.6	—	*(786)*

[a] Minimum intravenous dosage in rabbit eliciting fever greater than 1° F.

The second largest component is a tightly bound lipide fraction constituting between 13 and 28% of the various pyrogens. All attempts to remove the bound lipide completely have resulted in a complete loss of pyretic activity.

The phosphorus content varies from 0.4 to 3.1%. The phosphorus is probably present in the form of phosphate and may serve as a link between lipide and carbohydrate.

The nitrogen content of these "purified pyrogens" ranges from 0.7 to 2.2%. The character of the nitrogenous components has not been completely resolved. The status of the problem, based on the analytical results obtained on the most extensively studied products listed in Table IV, is as follows:

1. All investigators agree that hexosamine is present; however, this component does not account for all of the nitrogen.
2. All the products are reported to be free of nucleic acids.
3. Westphal and coworkers *(787)* have indicated that approximately one half of the nonhexosamine nitrogen in their *E. coli* preparation is associated with the lipide fraction.
4. There is a difference in reports relating to the presence of proteins, peptides, or amino acids in these preparations. Westphal and coworkers report that their *E. coli* pyrogen is completely free of these components without, however, indicating the tests used in obtaining such results. Shear's polysaccharide *(S. marcescens)* gave positive amino acid color tests *(352)* and also showed amino acid spots on chromatography of the hydrolyzate *(602)*. Amino acid spots have also been found by Ikawa and coworkers *(392)* on chromatograms of hydrolyzates of their *E. coli* preparation.

Pyrogens are now commonly referred to as bacterial polysaccharides, but they contain, in addition to the carbohydrate moiety, some lipide, phosphorus, and possibly peptide. Additional studies on purification, characterization, and comparison of pyrogens from various sources are essential to determine the limiting composition for pyrogenic activity and to determine what, if any, chemical differences exist. Although some such studies have already been conducted on pyrogenic lipopolysaccharides *(392–396, 481, 603)*, it is impossible to evaluate their contribution to the above problem because of the absence of pyrogenicity data on the fractions obtained.

Chemical Modifications. Within the past few years, several workers have prepared chemical derivatives of pyrogenic complexes. These include esters *(412, 618)*, ethers *(618)*, iodinated compounds *(659)*, and diazo derivatives *(36)*. It is noteworthy that the esters and ethers were reported to be nonpyrogenic *(412, 618)*. Work on acetylated pyrogens in the authors' laboratory indicates that reduction

in pyrogenicity is dependent upon the degree of acetylation *(36)*. These chemical derivatives may offer some clues as to the groups essential for pyretic activity, and provide some insight into the structure of pyrogens.

Prevention, Removal, and Destruction

Because pyrogen-producing microorganisms are air-borne, they can contaminate parenterals readily during any of the preparative steps. Three essentials must be fulfilled if contamination is to be prevented.

1. Rigid cleanliness in all operations.
2. A source of nonpyrogenic water *(120, 164, 194, 234, 305, 389, 457, 533, 573, 592–594, 657, 680, 699, 731, 732, 762–765, 769, 770)*.
3. Rapidity of operation, particularly in conducting sterilization immediately after bottling *(101, 374, 375, 734, 821)*.

Even if these three essentials are strictly observed, pyrogenic preparations may still result. This is attributed by most investigators *(99, 160, 164, 172, 175, 311, 454, 612, 733, 737, 742, 791)* to fever-producing contaminants in the chemicals and medicaments used in making up the parenterals; others contend *(74, 101, 197, 221, 225)* that the chemicals and medicaments are not involved. In 1942, Co Tui and Wright *(175)* claimed that 14% of the glucose, 7% of the saline, and 22% of the sodium citrate solutions which they prepared from nonpyrogenic water, but did not otherwise treat for pyrogen removal, were pyretic. In order to prevent such reactions, adsorption is routinely used by industry today. This method and many others for removing or destroying pyrogens have been studied, including heat, storage, enzymic action, additives, chemical treatment, and ultrafiltration.

Heat. Attempts to prepare nonpyrogenic solutions by the use of heat have received much attention, though the stability of pyrogens to heat is well documented *(29, 127, 280, 375, 406, 408, 567, 590, 652, 769, 770)*. Hort and Penfold *(374)* in 1911 demonstrated that neither autoclaving nor boiling was effective for destroying the fever-producing agent, while Seibert *(652)* noted that pyrogens resisted all but "long, drastic heating." Banks *(29)*, who made an extensive study of the effects of heat on the pyrexic agent, found that sterilization at a pressure of 20 pounds per square inch for 5 hours at pH 8.2 or for 2 hours at pH 3.8 successfully destroyed the thermogenic substance in solutions. Welch and coworkers *(775)* found that a temperature of 250° C. for 30 minutes was required to destroy a dried pyrogen from *Pseudomonas*. A patent *(384)* claims complete removal of pyrogens from amino acid solutions by autoclaving under nitrogen for 3 hours at 120° and a steam pressure of 15 pounds per square inch. Unfortunately, many parenteral solutions darken under extended heat treatment, and most of the specialized heating methods required for removal of pyrogens from solutions are commercially impractical because of either darkening or the time involved. Solid materials which are very stable to heat, such as sodium chloride, glassware, and syringes *(687, 775)*, may be made pyrogen-free by heating at an elevated temperature.

Storage. Several investigators *(100, 101, 160, 225, 348, 620, 687)* have noted that on standing some pyrogenic solutions become nonpyrogenic. There is considerable variation in reports concerning the time required for loss of the pyretic activity. Some solutions apparently lose activity in several weeks, while data are on record for a solution that was still pyrogenic after 3 years *(348)*. Some of this variability may be associated with the "pass-or-fail" type of animal test employed. Attention has been drawn to this variability *(527)*. The storage process has no practical application at present, as it is slow and unpredictable.

Enzymic Action. A United States patent *(583)* claims the destruction of pyrogens in protein hydrolyzates by the action of amylases over a period of several weeks. Inspection of the patent data shows that after treatment the solutions have less febrile activity than the starting materials, but the products in many cases would still be termed pyrogenic by U.S.P. standards. Rodney and Welcke *(619)* found that taka-diastase did not have any influence on several purified pyrogens, while Nesset and coworkers *(535)* reported that the pyrogenicity of *Pseudomonas* cells was unchanged by treatment with a number of different diastases.

Action of Additives. Polyvinylpyrrolidone (PVP), *(291)*, Chlor-Trimeton *(31,*

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71, 275, 546, 682), Antistine *(7)*, and Pyrilenzamine *(260)* have been reported to decrease the pyrexic activity when added to solutions. It is claimed that a vaccine which was pyrogenic in water was nonpyrogenic when dispersed in 5 to 15% polyvinylpyrrolidone. Thus, one would expect that polyvinylpyrrolidone itself would not be pyrogenic; this is not always the case. A recent publication *(682)* notes that addition of 10 mg. of Chlor-Trimeton to 500 ml. of blood effects a marked decrease in the number of pyrogenic transfusion reactions. While neither polyvinylpyrrolidone nor the antihistamines have any likely application for the common nutritional parenterals, both these and other additives may have certain special uses if their value is substantiated by future work.

Chemical Treatment. Destruction or attempted destruction of pyrogens has included chemical treatments involving acids *(36, 76, 164, 166, 218, 655, 708)*, alkalies *(36, 164, 166, 373, 559, 708)*, halogens *(109, 453, 708)*, quinones *(709, 710)*, reducing agents *(708)*, and oxidizing agents *(116, 132, 375, 490, 708, 718)*.

ACIDS AND ALKALIES. While both an acidic and an alkaline environment appear to be detrimental to the fever-producing substance, little practical use is made of this treatment for pyrogen destruction. Various acidic treatments have been used: Co Tui and coworkers *(164, 166)* boiled solutions 0.5 hour with 0.1*N* hydrochloric acid, Bharucha *(76)* used 0.01*N* hydrochloric acid, and a Hungarian patent *(218)* employs heating with cyclic or heterocyclic acids. It has been noted that heating pyrogenic solutions with 0.1*N* sodium hydroxide *(164, 166)* completely depyrogenizes them. A patent *(373, 559)* claims that heparin solutions are made pyrogen-free without loss of activity by treatment with alkali at pH 12 to 14 for 18 hours at 37°. In the authors' laboratory *(36)* room temperature treatment above pH 10 or heating in acidic environments rapidly destroyed a pyrogen from a *Pseudomonas* species.

HALOGENS. Attempts to destroy the fever-producing agent by treatment with chlorine *(109)*, bromine *(708)*, or iodine *(459, 708)* have proved unsuccessful. This is perhaps accounted for by the fact that the lipide portion of several pyrogens is apparently unsaturated and can add halogen without affecting the pyrexic activity. Treatment of a pyrogen from *S. marcescens* with tagged iodine *(660)* yielded an addition product with a stable iodine linkage. Iodination studies on a pyrogen from a *Pseudomonas* species *(36)* produced an iodo derivative with pyrogenic activity approximating the original.

QUINONES. Suzuki *(709, 710)* reported that a number of quinones were extremely effective for eliminating the pyrogenicity of glucose solutions. Further study on the practicality of this approach is necessary.

REDUCING AGENTS. Pyrogenic dextrose solutions have been treated with the following reducing agents *(708)*: zinc and hydrochloric acid, zinc and sodium hydroxide, stannous chloride, sodium bisulfite, zinc powder, tin and hydrochloric acid, potassium ferrocyanide, and magnesium and ammonium hydroxide. Suzuki concludes that these reducing treatments are not effective for destroying or removing the thermogenic factor.

OXIDIZING AGENTS. Oxidizing agents appear to be effective for destroying pyrogens; many have been examined, including acidic, alkaline, and neutral permanganate *(708)*, dichromate *(708)*, nitric acid *(708)*, selenium dioxide *(708)*, hypochlorite *(132)*, and hydrogen peroxide *(116, 375, 490, 718)*. Of these, hydrogen peroxide, which can be completely removed without the introduction of any new ions, has been most widely studied. In 1911, Hort and Penfold *(375)* found that *E. typhosa* and *Ps. aeruginosa* cells lost their fever-producing effects when washed with dilute peroxide. Taub and Hart *(718)* and Menczel *(490)* were able to prepare nonpyrogenic solutions of saline and saline-dextrose by boiling for 1 hour with 0.1% hydrogen peroxide. Because hydrogen peroxide has possible applicability to saline, dextrose, protein hydrolyzate, and other parenteral solutions, it appears worthy of further study.

Ultrafiltration and Adsorptive Techniques. The most important methods of removing pyrogens make use of ultrafiltration and adsorptive techniques. A wide variety of substances for adsorbing or filtering out pyrexic materials have been studied, including alumina *(708)*, aluminum powder *(164)*, asbestos *(76, 112, 164, 167, 168, 172, 173, 175, 270, 477, 599, 688, 736, 739, 775, 795, 831)*, bentonite *(708)*, carbons *(73, 76, 100, 101, 114, 132, 164, 218, 219, 289, 290, 356, 382, 385, 448,*

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458, 490, 559, 568, 708–710, 718, 733, 735), cellulose and oxidized cellulose *(708, 738)*, collodion *(408)*, filters (bacterial and others) *(100, 101, 112, 164, 167, 168, 173, 270, 406, 477, 599, 688, 718, 736, 739, 795, 831)*, glass *(100, 101)*, hydroxides of aluminum, copper, and iron *(458)*, ion exchange resins *(347, 356, 606, 688, 708)*, kaolin *(164, 734, 795)*, kieselguhr *(708)*, and starch *(708)*. Only asbestos and the carbons appear to have general applicability for this purpose. Co Tui's *(167, 168, 173)* pioneering work on the use of asbestos for the removal of pyrogens has been followed by many other publications indicating that asbestos may be used for removing the fever-producing materials from almost any parenteral solution. Asbestos has been used on solutions of dextrose *(167, 173, 175)*, inulin *(172, 270)*, penicillin *(599, 739, 775)*, plasma *(112, 477. 599. 688)*, protein hydrolyzates *(831)*, saline *(173, 175, 736)*, and serum *(688)* in addition to water alone *(168, 173)*. Because asbestos does not have as great a capacity as many activated carbons *(99, 831)*, most commercial usage probably favors the carbons, though such depyrogenizing techniques are trade secrets. Carbons have been used in the treatment of water alone *(100, 101, 382, 448, 735)* as well as for solutions of dextrose *(718, 735)*, inulin *(270)*, varied pharmaceuticals *(73, 76, 100, 101, 132, 289, 290, 568)*, saline *(718, 735)*, and streptomycin *(385)*. Acid-treated carbons *(290, 735)* appear to be most widely used, but all carbons have as a disadvantage the difficulty of removing colloidal traces from the treated solution. This difficulty is particularly pronounced with protein hydrolyzates *(36)*. Carbons cannot be used where the adsorption of the medicaments or chemicals in the parenterals is pronounced, but, as only small quantities are usually required for pyrogen removal, carbon is applicable to most solutions.

Tests for Pyrogens

Physical and Chemical Tests. The U. S. Pharmacopoeia *(580)* and British Pharmacopoeia *(102)* contain animal assay methods for parenterals in which the temperature response in rabbits under standardized conditions is used to classify solutions as pyrogenic or nonpyrogenic. Since the cost and time involved in the animal assays are considerable, more rapid and simple tests would be desirable. A number of workers have reported physical and chemical tests for pyrogens aimed at rapidly separating the definitely nonpyrogenic solutions from those that are suspect. All of these tests are actually assays indicative of contamination rather than true methods of determining the fever-producing substance. Nevertheless, if proved acceptable, such tests could cut down the number of solutions requiring animal assay to a small percentage.

Bacterial Measurements. The belief that a bacterial measurement could be correlated with febrile response has been proved false. A test showing the absence of live bacteria in a parenteral, while certainly necessary, cannot be trusted to rule out conclusively the presence of pyrogens, as many sterile solutions are still pyrogenic. Hort and Penfold *(375)*, Seibert *(652)*, Rademaker *(592)*, and Probey and Pittman *(590)* have all pointed out that a bacterial count of the water will not indicate the quantity of fever-producing substance which is present. While autoclaving readily destroys bacteria, it is relatively innocuous to most pyrogens, and thus measurement of microorganisms in parenterals cannot be used to prove the absence of febrile agents.

Electrical Conductivity. Measurement of the electrical conductivity has been suggested as a pyrogen test for water *(164)*. As any ionic substance influences the electrical conductivity, this test has the obvious difficulty of having many interferences; therefore, it is not utilized at present.

Ultraviolet Absorption at 2650 A. Measurement of the ultraviolet absorption at a wave length of 2650 A. has been proposed as a means of detecting pyrogens. Hatta and coworkers *(356)* found that, in general, pyrogenic solutions absorb more strongly at this wave length than nonpyrogenic ones. However, they report that many solutions which gave a positive test were not pyrexia-producing in rabbits, while some solutions on which a negative test was obtained were found to be pyrogenic. Nucleic acids *(131)* absorb strongly at the wave length used in this test and it is likely that actually the constituent cellular nucleic acids are being measured. In the authors' laboratory *(36)*, a purified pyrogen from a *Pseudomonas*

species containing no nucleic acids failed to exhibit an ultraviolet peak at 2650 A., while the nucleic acids separated in the purification did absorb strongly.

CHEMICAL AND COLOR TESTS. Several chemical and color tests for pyrogens have been suggested. The Carter permanganate test for distilled water has been examined by several investigators *(120, 164, 568, 731)*. In this test, which is a modification of the U.S.P. test for oxidizable substances, 100 ml. of the sample is boiled with 10 ml. of sulfuric acid and 0.1 ml. of 0.05*N* permanganate solution. If the solution remains colored after boiling, presumably pyrogens are not present. As the test procedure does not discriminate between oxidizable substances, it cannot be used where other organic materials are present.

Menczel *(490)* has offered a color test for pyrogens which is a modification of Feigl's *(254)* ferric chloride–potassium ferricyanide reaction for hydrogen peroxide. According to the test procedure, 100 ml. of solution plus 10 drops of a reagent made by combining equal quantities 0.4% ferric chloride solution and 0.8% potassium ferricyanide produce a blue color or tint if pyrogens are present. The color is apparently given by readily oxidizable substances, but dextrose does not interfere if the color is examined within 10 minutes. Menczel does not report the range of pyretic activity corresponding to a positive or negative reaction, but as this test is apparently applicable to many common parenteral solutions, it appears to warrant further study.

Several Japanese investigators *(429, 708–710, 742)* have reported the use of tetrabromophenolphthalein ethyl ester (TBP) for the determination of pyrogens. Uraguchi *(742)* and Suzuki *(708)* claim a correlation between the tetrabromophenolphthalein ethyl ester color test and febrile tests in animals. The same reagent has been used for the microdetermination of proteins *(255, 398, 399)* in amounts as small as 0.1 γ, so it appears that what is actually being measured in this color test is small quantities of proteinaceous material in the contaminated solutions.

Several other color tests have also been applied to pyrogenic materials. These include the following protein or carbohydrate tests: biuret *(353, 543, 663, 668)*, Millon *(353)*, ninhydrin *(353)*, xanthoproteic *(353)*, Fehling *(356)*, Benedict *(353)*, and Molisch *(101, 164, 204, 353, 663, 668)*. The latter test has shown the most promise and probably warrants more examination, as the active factor is largely carbohydrate in nature. The purified polysaccharide from *S. marcescens* gives a color reaction with toluidine blue, just as heparin does *(517)*. Determinations of total nitrogen *(653)*, volatile nitrogen *(592)*, and phosphorus *(133)* have also been employed, but without any successful correlation with pyrogenicity.

While the physical and chemical tests are not specific for the fever-producing factor, certain cellular constituents will always be present in a contaminated solution if they have not been removed by prior treatment. Thus, any procedure used to measure cellular constituents in small enough concentration may find applicability as a screening test, provided that no interference is given by the solution tested. Further study of purified pyrogens may reveal specific properties on which determinations of the true pyrogenic factor may be based.

U.S.P. Pyrogen Test. The increasing use of parenteral therapy in its many forms during the past several decades has drawn particular attention to the problem of subtle pyrogenic contamination in parenteral products and the possibility of thermal reactions following the administration of such products to humans. To avoid inadvertent fever, an official test procedure, which sets minimal standards for product acceptability, has been adopted.

The fundamental researches of Wechselmann *(769, 770)*, Hort and Penfold *(374–380)*, Jona *(408)*, Penfold and Robertson *(572)*, Seibert and coworkers *(93, 652–657)*, Rademaker *(592–594)*, Banks *(29)*, Co Tui and coworkers *(164–175)*, Walter *(762–765)*, and Nelson *(533)* led to the first U.S.P. collaborative study on pyrogens. This study, which was described by McClosky and others *(473)*, resulted in the official procedure which first appeared in the 12th revision of the U. S. Pharmacopoeia *(579)*. The test involves injection of the parenteral substance into the marginal ear vein of the rabbit under specified conditions and rectal measurement of temperature. Essentially the same test appears in U. S. Pharmacopoeia XIV *(580)*. The latter issue contains almost 100 individual monographs on official injections that must meet the requirements of the pyrogen test.

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A miscellany of limitations and requirements are specified in the official test. Most of these are based on well established fact; a few are not.

TEST ANIMAL. Bacterial pyrogens are stated to elicit temperature rises in men, dogs, and rabbits, but not in mice, rats, guinea pigs, or chicks *(725)*. However, in addition to rabbits, Weger *(772)* observed a response in mice and horses. Adoption of the rabbit as the standard animal in the U.S.P. test was based largely on the studies of Co Tui and Schrift *(169)*, who reported the rabbit to be three times less sensitive than human beings. The rabbit logically was chosen over the dog because it is smaller, less costly, and more sensitive. Use of the test over many years has demonstrated excellent agreement between clinical and laboratory data and has established the reliability of the rabbit. Recent studies by Dare and Mogey *(193)* indicate the sensitivity of the rabbit can range from one third to seven times that of man, depending upon the manner in which the test is conducted.

Hort and Penfold *(376)* found that the guinea pig will respond to pyrogens, but not reliably; however, Alexander and others *(5)* have shown that the guinea pig is sensitive to a pyrogen from a *Pseudomonas* species and might be satisfactory for use in a standardized pyrogen test. Economic advantages would result from the use of this smaller animal, but its acceptance for the test demands additional experimental work to establish responsiveness to various pyrogens and to correlate such responsiveness with clinical data.

RABBIT SELECTION. The official test states that the rabbits must be healthy, must be maintained on a uniform diet for 1 week, and must show no weight loss. Ott *(560)* and Tennent and Ott *(725)* have shown that test sensitivity is improved by a preliminary selection made on the basis of similarity in normal temperature and body weight, followed by a second selection for individual sensitivity on the basis of the slope of the dose-response relation and stability of the base line.

SEX OF ANIMALS. No limitation is made in the U.S.P. test on rabbit sex. Tennent and Ott *(726)* used only male rabbits in evolving a quantitative assay procedure. Dare *(192)* found that when males are used exclusively, the dosage-response curves are higher. He *(191)* also tried equal numbers of male and female rabbits in a mixed colony but did not analyze for differences. Most other investigators have used virgin does exclusively. On the basis of present knowledge *(319)*, the most consistent results would be expected from the use of rabbits of a single sex to avoid emotional stimuli that might disturb the labile rabbit thermoregulatory system.

HOUSING, FEEDING, AND EMOTIONAL FACTORS. The first U.S.P. collaborative study reported by McClosky *(473)*, and the work by Welch and others *(774)*, established the official conditions for housing test animals at constant temperature and humidity, in individual cages, and relatively free from excitement. Official conditions also stipulate that food should be withheld beginning 1 hour before the first temperature reading and during the entire test. The initial fasting period may not be sufficient *(222)*. Kobayashi *(426)* has reported that rabbit temperature is notably affected by food, and requires between 1 and 1.5 hours for stabilization after initiation of fasting. Body temperature is reported to decline an average of 0.5° C. during the first 60 to 90 minutes after removal from the cage *(505)*. Grant *(319)* has made particular issue of emotional factors and their effect upon the test results; hormonal links may be involved.

RABBIT SIZE. The official test specifies a minimal weight of 1500 grams for the test rabbits. No upper limit is provided. Smith *(687)* recommends that rabbits be discarded when their weight reaches 4000 grams. Probey and Pittman *(590)* reported that rabbits weighing 2000 to 3500 grams gave much more uniform results than smaller animals. Tennent and Ott *(725)* have shown that below 2000 grams, animal sensitivity is lower, slope of the dose-response relation is less steep, and the individual variation is larger than above this weight. The most practical range appears to be 2000 to 4000 grams.

NORMAL TEMPERATURE. The official specifications provides for use of rabbits in the temperature range of 38.9–39.8°. The average normal temperature of the rabbit was reported by Freund *(281)* to be 38.6–39.6°, by Bock *(85)* to be 38.6–39.9°, by Moore *(507)* to be 39.4°, by Frothingham and Minot *(284)* to be 39.9°, by Seibert *(655)* to be 39.05°, by Kobayashi *(426)* to be 39.26°, and by Dorche *(223)* to be

38.9–39.7°. Under the test conditions employed in the first U.S.P. collaborative study *(473)*, 85% of the normal rabbit temperature readings fell between 38.9° and 39.7°. It was demonstrated by Molitor and others *(505)* that animals with low normal temperatures generally respond to the injection of a pyrogenic substance with a higher rise in temperature than rabbits with high normal temperatures. Thus, test sensitivity could be improved by using animals on the low side of the normal range. Hort and Penfold *(375)* and Probey and Pittman *(590)* have shown that pyrogen-free saline induces a depression in the normal rabbit temperature. Subtle masking of pyrogenicity of borderline medicaments dispersed in saline could result because of the competitive effects. The true "baseline" temperature of such animals has been stated to be the hypothermic level observed in the pyrogen-free saline control *(590)*.

RESTRAINT. No U.S.P. recommendation exists. With the use of automatic temperature-recording equipment, it has become common practice to secure the test animals in stanchions during temperature measurement. Molitor and others *(505)* employed moderate restraint and observed rectal rabbit temperatures approximately 0.2° to 0.3° C. lower than those encountered when stanchions were not used. Similarly, Tennent and Ott *(725)* employed a box confining the rabbit closely but not uncomfortably and reported temperatures about 0.5° C. lower. Dare *(190)* has shown that when the degree of restraint is minimal, the response is maximal. Dare and Mogey *(193)* have presented convincing evidence to show that the extent of restraint can alter sensitivity of the rabbit to measure threshold pyrogenicity, so that the rabbit will appear to be one third to seven times as sensitive as the human to pyrogens. Grant *(319)* has observed that with frequent use, many rabbits can be trained to tolerate mild restraint without disturbance of thermoregulation. For practical conduct of the official test, specific recommendations concerning the degree of restraint are needed.

TEMPERATURE MEASUREMENT. The U.S.P. requires the use of a clinical rectal thermometer or other measuring device inserted beyond the internal sphincter. Molitor and others *(505)* and Kuna and others *(443)* have observed that insertion of the rectal thermometer is likely to cause a rise in rabbit temperature reaching a peak in 60 to 90 seconds and returning to normal in 10 to 30 minutes. In the interest of economy, many pharmaceutical firms have abandoned the slow, time-consuming, and costly method of taking temperatures with fragile, glass-stemmed thermometers, and have turned to thermocouples or resistance thermometers with automatic recording equipment instead. It is likely that the human error is substantially decreased and that the lessening of emotional stimuli by the absence of handling serves to improve the quality of the test. Studies on automatic recording devices *(223, 687, 725)* indicate that thermocouples or resistance thermometers should be inserted to a depth of 7.5 to 10 cm. for reproducible results; official specifications would be improved by inclusion of this range.

PRETEST. U.S.P. specifications require that four rectal temperatures be taken at 2-hour intervals, 1 to 3 days before use, such temperatures to fall in the normal range. Animals which have not been used for more than 2 weeks are subject to the same pretest. It has commonly been observed that fluctuations in rabbit temperature associated with handling and excitement become less pronounced as the animals become more accustomed to the procedure. Under conditions of automatic recording with restraint, additional conditioning is indicated. Tennent and Ott *(725)* have described a mock test procedure in which the number of animals rejected seldom exceeds 10%. It would be desirable to adopt a pretest that more nearly approximates the actual conditions used in the pyrogen test rather than the somewhat unrelated pretest now used.

VOLUME OF INJECTION. By a comparison of thermal effects in humans and rabbits, Co Tui and Schrift *(169)* concluded that to test intravenous solutions for human use, 50 to 100 ml. per kg. of the parenteral material must be given to rabbits. Lees and Levvy *(448)* used a dose of only 20 ml. per rabbit, Welch and others *(774)* reported an injection volume of 10 ml. per kg., the first U.S.P. collaborative study *(473)* involved the use of 3 ml. per kg., and Yokoe and others *(815)* found that 10 ml. per kg. gives more accurate results than 2.5 or 5.0 ml. per kg. The official test specifies an injection volume of 10 ml. per kg. The slope of the line relating temperature rise to the logarithm of the dose has been claimed to be very

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shallow, so that small changes in dose have little effect on the level of the response *(687)*. It has been suggested that the volume of solution used in the test animal should be related to the volume per kilogram of body weight of the material used in the clinic.

TEMPERATURE OF FLUIDS. The official test specifies that the product to be tested should be warmed to approximately 37° C. However, Smith *(687)* is satisfied that the injection of 25 ml. of distilled water at room temperature has no noticeable effect on the recorded temperature of the rabbit. Engelund and Terp *(242)* injected solutions in the temperature range of 18° to 37° C; identical results were obtained at the extremes of this range. It appears that the injection of fluids from room temperature to 37° should be acceptable.

FREQUENCY OF USE. The official test specifies that rabbits must have a rest period of not less than 48 hours. There is no published information on the development of tolerance in animals repeatedly receiving subfebrile amounts of pyrogenic materials. However, a great deal of information is available correlating rabbit response with repeated administration of pyrogenic doses. The conclusions differ considerably. Wiley and Todd *(794)*, Weger *(772)*, and Milulaszek and others *(502)* found no change in the response of rabbits used repeatedly. Stewart *(698)* observed an increase in sensitivity in female rabbits injected daily for 6 days, followed by a decrease. Molitor and others *(505)* reported a small decline in response "associated with handling and excitement" which decreased "with animal conditioning." The first U.S.P. collaborative study *(473)* and investigations by Beeson *(45, 46)*, Grant *(319)*, Tennent and Ott *(725, 726)*, Dare *(190)*, Ogasawara *(547)*, Kobayashi and others *(428)*, and Fujitake *(285)* have shown that rabbits become refractory very rapidly. Peak refractoriness is probably attained in 7 to 10 days *(725)* and original responsiveness is regained slowly. Rest periods of 3 weeks *(725)* to longer periods *(190, 547)* including 8 months *(190)* have been reported to be necessary. Present knowledge indicates that the official rest period of 2 days may be satisfactory if the test animals do not become febrile *(355)*; however, if a parenteral product is adjudged pyrogenic, the animals used in the test probably should rest for 2 to 3 weeks. Further study is required on the length of time.

A substantial amount of research has failed to elucidate the mechanism of the tolerance phenomenon. Perry *(575)* and others *(45, 147, 279, 509, 537, 753, 774)* have studied circulating antibodies, a number of investigations *(46, 509)* have involved the functional capacity of the reticuloendothelial system, interaction of the pyrogen with some plasma component has been investigated *(142, 246–250, 317, 320–322, 324, 327, 328, 452, 453)* and a miscellany of other studies *(312, 324, 575)* have also been conducted.

LIMITATIONS. Comparatively little attention has been devoted to the problems involved in testing parenteral substances capable of masking pyrogenicity. The present test limits rabbits to single usage for allergenic substances. Various other medicaments such as calcium gluconate, procaine, sodium citrate, strophanthin, chlorpromazine, and certain hypnotics and anesthetics *(36, 135, 136, 193, 226, 358, 791, 827)* have been observed to lower rabbit body temperature, inhibit the febrile response, or in some manner mask the test result. False results may be obtained when such substances are present.

TEST INTERPRETATION. The official test states that the test is positive if two or three animals show an individual rise in temperature of 0.6° or more above normal. If only one does or if the sum of the rises for all three exceeds 1.4°, the test is repeated using five rabbits. It is positive if two of the five show rises of 0.6° or more above normal. Some of the variability in the test may be associated with the "pass-or-fail" interpretation given to it. Strongly pyrogenic solutions are readily detected, but subtle contamination may result in the administration of doses at or near the rabbit's pyrogenic threshold. Attention has been directed to the variability in response *(527)* which complicates the problem of unequivocally placing the borderline parenteral product in the pyrogenic or nonpyrogenic category. When a retest is demanded by the present specifications, only the retest animals are employed in appraising the result. It would seem more logical to use all of the animals.

QUANTITATION. No specification exists, but efforts have been made to place the pyrogen test on a quantitative basis *(134, 199, 505, 560, 561, 726)*. Tennent

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and Ott *(725)* in particular have accumulated much detailed information to establish the concept that the pyrogenic response is a linear function of the logarithm of the dose. Conversely, Dawson and Todd *(199)* after a careful attempt to quantitate the pyrogen test by calculating correlation coefficients for a number of measurement pairs, concluded that temperature response in the rabbit is not an accurate method for quantitative assay.

Further study of such problems as rabbit sensitivity and selection, effect of restraint, and the tolerance phenomenon and its mechanism would be expedited by the availability of a primary pyrogenic standard *(381, 526, 575)*. Difficulty exists in choosing a representative standard, as pyrogens are elaborated by a number of bacteria. Much is yet to be learned about the test, but the adoption of a pyrogenic standard and its use in several well-integrated, collaborative studies should eliminate many of the problems and result in a test of a more quantitative nature. The Expert Committee on Biological Standardization of the World Health Organization has initiated a preliminary study involving Shear's polysaccharide *(S. marcescens)* and a preparation from *Proteus vulgaris* to determine whether either of these could serve as a pyrogenic standard.

Other Biologic Tests. Studies on experimental animals indicate that, in addition to a direct action on certain target organs, small doses of pyrogens are capable of stimulating the pituitary-adrenal axis *(420, 577)*. Endocrine effects have been observed in man and laboratory animals *(200, 312, 430, 541, 782, 799)*. Some of these responses have been investigated as a means of detecting pyrogens.

CHANGES IN WHITE BLOOD CELL COUNT. Marked hematologic changes are observed upon injection of pyrogens into animals *(56, 61, 86, 89, 92, 97, 130, 141, 165, 169, 174, 199, 200, 203, 205, 211, 222, 250–252, 367, 386, 421, 455, 464, 493, 494, 504, 510, 512, 550, 551, 590, 615, 685, 693, 694, 721, 776, 789, 799, 816, 828)*. The typical response is an initial sharp decline in the white blood cell count (a leucopenia) followed by a pronounced increase (a leucocytosis). The leucopenia usually occurs within 1 hour after injection, usually with white blood cell decreases of 50% or more. The leucocytosis occurs in 3 to 24 hours with three- to fivefold increases in the white blood cell count. Various workers have recommended that the leucopenia *(130)* or leucocytosis *(816)* rather than temperature change be used as a test for pyrogens. Other investigators *(59, 92, 97)*, however, did not find leucocytic changes as reliable a guide as temperature elevation.

While this method holds some promise as a test for pyrogens, additional work, including standardization of animals and methods, would be required before this test could attain U.S.P. status. Some of the following problems would have to be overcome:

1. The decline in the white cell count is so sharp that the minimum is easily missed unless frequent samples are taken.
2. The onset and duration of the leucocytosis are variable, requiring numerous samples to avoid inconsistent results.
3. The choice of test animal demands further study. The rabbit, dog, and cat have all been used, leading to the following conclusions: The rabbit, which has been used most frequently, exhibits considerable fluctuation in its normal white blood cell count *(222)*. The dog, which has a more stable white blood cell count baseline, does not show as great a response to pyrogens as does the rabbit *(171)*. The cat appears to have a reliable baseline and responds well to small doses of pyrogens *(36 799)*. Insufficient work has been done on this animal to date.

SECRETORY AND EXCRETORY CHANGES. Decrease in adrenal cholesterol *(541)* and lipide *(541)*, and increase in uropepsinogen excretion *(788)*, have been observed after the injection of pyrogens. The relatively high doses required to elicit these responses render them impractical for routine pyrogen testing. The uniform difficulty associated with the foregoing measurements is their lack of specificity. Some of the responses can be elicited by nonpyrogenic substances. It has also been reported that white blood cell changes do not correlate with temperature changes *(199)*. Furthermore, the blood changes have not been studied as comprehensively as the febrile response, and the association between such responses in experimental animals and clinical acceptability of a parenteral product is not clearly established.

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Biologic and Clinical Studies

Although this review is primarily concerned with those aspects of the pyrogen problem (isolation, chemical nature, removal, destruction, detection, and quantitation) of immediate concern to those who produce or are engaged in the use of parenteral products, attention is also directed to the voluminous literature dealing with fundamental physiologic studies on pyrogens. In referring to this extensive literature, much of the work involving "nonspecific, foreign protein reactions" is deliberately omitted because of the conviction that it is virtually impossible to duplicate many of such materials; hence, such information is not of practical significance. Most of the studies cited are concerned with reasonably well characterized vaccines or pyrogenic polysaccharide fractionation products of varying degrees of purity.

Fever is the commonly recognized physiologic response following administration of a pyrogen. Attention has been directed in the discussion of the U.S.P. pyrogen test and other biologic test methods to characteristic changes in the white blood cell count, to the tolerance phenomenon, and to changes in the biochemical status of the adrenal gland. A miscellany of additional studies on white blood cells and other hematologic changes have been conducted *(30, 32, 46, 58, 62, 64, 66, 70, 75, 98, 170, 192, 193, 199, 201, 202, 206, 212, 224, 244, 246–249, 256, 274, 283, 308, 315, 317, 319, 320, 322, 411, 413, 414, 423, 426, 439, 442, 456, 482, 483, 485, 487, 489, 503, 511, 512, 517, 549, 554, 597, 617, 644, 658, 669, 748, 752, 778, 782, 792, 793, 796, 797).* The pituitary-adrenal axis is probably involved in the response to pyrogens, either via a generalized "alarm" reaction or because of a more direct effect. Studies have involved this system as well as other endocrine glands *(162, 200, 215, 216, 312, 430, 503, 541, 582, 597, 713, 714, 782, 784, 799, 805).* A number of fundamental researches have been concerned with cellular and tissue changes *(328, 360, 446, 522, 523, 587, 636, 641, 700, 702, 801, 804, 805),* cardiovascular changes *(9, 10, 39, 86–88, 206, 207, 449, 450, 483, 584, 721, 771, 804),* metabolic effects *(162, 335, 438–441, 496, 571, 644),* renal and urinary effects *(137, 161, 365, 412, 487, 635, 715, 789),* respiratory changes *(233, 318, 323, 325, 326, 336, 571, 596, 799, 802),* mechanism *(18, 33, 47, 57, 65, 86, 129, 140, 141, 200, 207, 279, 296, 312, 317, 320, 322–325, 335, 354, 415, 461, 462, 542, 575, 585, 595, 596, 600, 601, 649, 689, 691, 694, 697, 701, 757, 777, 789, 818),* gastrointestinal changes *(82, 170, 478, 497, 530, 532, 558),* and other physiological and biochemical alterations *(54, 55, 75, 141, 147, 148, 198, 243, 247, 253, 315, 330–332, 335, 358, 397, 425, 471, 472, 596, 670, 755–757, 767, 773, 799).* Microbiologic researches have elucidated the many sources of pyrogens listed above in the discussion of isolation and chemistry. In addition, a number of investigations have dealt with the effect of pyrogens on infectious organisms both in vitro and in the animal body *(301–303, 604, 621, 686).* The influence of pyrogens on immunologic relationships has been a particularly active field *(16, 19, 23, 25, 45, 48, 51, 57, 60, 62, 75, 77, 80, 81, 86, 90, 91, 94, 105, 106, 124, 127, 142, 147, 180–183, 195, 196, 203, 208, 209, 212, 220, 229, 231, 232, 245, 248, 251, 256–258, 272, 279, 292, 294, 312, 339, 341, 357, 369, 401, 407, 409, 416, 445, 467, 482, 509–511, 513, 514, 516, 537, 547, 551–554, 556, 565, 627, 628, 639, 672–678, 686, 695, 703, 706, 712, 716, 743, 746, 785, 790, 808, 817, 819, 822, 823, 825, 826).* Tumorlytic action of pyrogens in laboratory animals is well documented. Hemorrhage and necrosis in animal tumors have been demonstrated with a number of crude vaccines as well as with highly purified pyrogenic polysaccharide complexes *(8, 10, 11, 14–17, 38–44, 94, 103, 119, 180–183, 214, 217, 228–230, 265, 286, 292, 293, 313, 339, 351–353, 390, 391, 401, 402, 410, 446, 474, 524, 607, 660–669, 672, 676, 677, 689, 760, 772, 780, 790, 819, 820, 822, 823, 825, 826).* Recently, the possibility of effecting regeneration in the central nervous system with pyrogens aroused a great deal of research activity. A number of studies in experimental animals have demonstrated some structural regeneration but questionable functional regeneration following severance of nerve fibers in the central nervous system *(2, 28, 128, 143–145, 277, 307, 370, 444, 463, 476, 647–649, 701, 798, 800, 803).* Although pyrogens in the extremely low dosage required to produce a febrile response are apparently innocuous, a number of reports describe pathologic changes in laboratory animals *(6, 11, 30, 43, 63, 81, 115, 170, 180-183, 201, 214, 216, 256, 258, 273, 286, 313, 339, 349, 391, 430, 439, 449, 467, 483, 492, 498, 508, 509, 514, 548, 555, 582, 677, 689, 729, 730, 743, 757, 780, 820, 824).* Excessive dosage or impurities may be contributory factors.

With the wide spectrum of physiologic activities associated with pyrogens, it is not surprising to find that they have had equally wide therapeutic application. It has been reported that they are effective in allergies *(22, 26, 34, 259, 262–264, 266, 314, 337, 340, 368, 404, 423, 475, 479, 589, 597, 598, 632, 639, 646, 681, 712, 759, 761, 766, 768, 809–811, 830)*, dematoses *(22, 138, 149, 185, 213, 259, 334, 388, 417, 418, 475, 479, 622, 633, 679, 705, 740)*, certain ophthalmologic conditions *(20, 113, 146, 186, 298, 437, 538, 539, 569, 574, 751, 779)*, arthritis and rheumatism *(122, 178, 179, 269, 500, 501, 525, 581, 638, 650, 696, 707, 717, 740, 758)*, infectious diseases *(1, 4, 51, 68, 72, 117, 118, 137, 184, 213, 271, 276, 278, 287, 329, 338, 363, 364, 371, 383, 403, 416, 419, 424, 434, 436, 447, 470, 499, 509, 515, 521, 537, 576, 591, 621, 626, 633, 636, 643, 671, 695, 696, 717, 722, 723, 728, 740, 744, 807, 829)*, cardiovascular diseases, particularly malignant hypertension *(12, 52, 83, 95, 121, 189, 309, 310, 403, 486, 488, 562–564, 690, 719, 720, 812, 813)*, gastrointestinal involvements *(3, 200, 306, 387, 531, 557, 588, 633, 634, 642, 806)*, psychotic conditions, especially neurosyphilis *(13, 21, 26, 29, 213, 227, 251, 252, 262, 288, 297, 304, 364, 386, 431, 432, 466, 480, 495, 536, 570, 586, 609, 614, 633, 683, 684, 699, 727, 749, 771, 781)*, central nervous system involvements, such as severed spinal cords, paralyses, and spasticities *(4, 21, 26, 28, 29, 68, 104, 118, 138, 177, 213, 278, 282, 288, 386, 403, 405, 423, 468, 484, 521, 591, 605, 610, 621, 633, 643, 692, 740, 750, 781, 803)*, neoplastic diseases *(24, 35, 84, 103, 139, 151–159, 163, 176, 187, 188, 214, 235–240, 267, 268, 333, 343–346, 350, 360–362, 372, 406, 451, 459, 460, 465, 528, 529, 545, 607, 608, 629, 630, 637, 659, 660, 711, 760)*, and other disorders *(37, 49, 123, 316, 359, 414, 435, 491)*. Undesirable or toxic effects have been associated with pyrogen therapy by some investigators *(1, 50, 96, 366, 433, 544, 707, 771)*. Much work still remains to assess properly the value of pyrogens in our therapeutic armamentorium.

A number of review articles and symposia, which cover particular phases of the chemical, biological, and therapeutic aspects of pyrogens, are available *(59, 104, 123, 210, 241, 261, 295, 400, 422, 506, 529, 534, 540, 578, 614, 623, 640, 740, 741, 781, 811)*.

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Using the Literature on the Stability of Pharmaceutical Ingredients

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Pharmaceutical manufacturers have become increasingly aware of the need for early introduction of their products to the physician. One development problem is the stability of the product, and one way of speeding the solution of this problem is use of the literature.

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New formulations constitute one of the great challenges to the pharmaceutical manufacturer, for problems arising in the development of new drugs must be solved quickly. This urgency stems from the need to provide the physician with new drugs at the earliest moment and to maintain an advantageous position in a highly competitive field. One of the hurdles that bar the way to prompt introduction of a drug is product stability, which has become increasingly difficult to achieve as products have become more complex.

When several therapeutically active drugs are combined in one preparation—e.g., aspirin-phenacetin-caffeine, vitamin B_{12}–intrinsic factor—the stability problems are multiplied because the medicaments may react chemically with each other or indirectly affect the stability of other ingredients. Even when there is only one active ingredient, it is rarely possible to prepare a stable product by simply dissolving the drug in a solvent.

How Literature Can Help

The aim here is to describe the use of the literature as an aid to solving stability problems—the type of data available and where and how it may be found. In developing a new formula, full utilization of published information helps reduce experimental work on stability.

Suppose, for example, one is given the problem of developing an oral liquid multivitamin preparation. The skeleton formula might be something like that shown in Table I.

Table I. Skeleton Multivitamin Formula

Ascorbic acid	75.0 mg.
Thiamine HCl or mononitrate	2.5 mg.
Niacinamide	20.0 mg.
Riboflavin	2.0 mg.
Vitamin B_{12}	5 γ
Pyridoxine	0.5 mg.
Vehicle to make	15.0 cc. (daily dose)

The finished preparation must ensure uniform dosage and optimal absorption of the active ingredients, be acceptable to the patient and physician, and remain stable for a shelf life of 2 to 3 years. In developing a suitable formulation for these drugs, some of the problems are selection of solvents and solubilizers to dissolve all components, buffers to regulate pH, antioxidants, preservatives to prevent bacterial and mold growth, sweetening and coloring agents, and aromatics. Each ingredient should itself remain stable, and not cause decomposition of the active ingredients or interfere with their therapeutic efficacy. In short, stability is associated with every stage of development.

Stability problems may arise from a number of causes, which may be chemical, physical, or biological in nature (Table II).

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE;
Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Table II. Causes of Drug Instability

Chemical	*Physical*	*Biological*
Oxidation	Insolubility	Bacterial and fungi contamination
Reduction	Separation	Insect contamination
Hydrolysis	Loss or gain in moisture content	
pH change	Change in physical state	
Double decomposition		
Racemization		

The best approach to work on product stability is first to review the pertinent literature on the behavior of each ingredient. One of the compounds in the tentative formula of Table I, ascorbic acid, may be taken as an example. The stability problem here is decomposition caused by oxidation. This decomposition is accelerated by the presence of atmospheric oxygen, light, heat, and traces of copper, iron, and manganese. In reviewing the literature, then, one should look for any information on retarding or preventing the oxidation of ascorbic acid—effect of solvents, pH, temperature, different kinds of light, other compounds, etc.

In approaching this problem, at least three literature sources should be considered: technical data from the manufacturer, journals, and patents. If the compound, like ascorbic acid, can be obtained from a bulk manufacturer, technical data from the manufacturer may be especially valuable, as they may not be available elsewhere. These three sources of stability information may be supplemented by other sources (Table III).

Table III. Sources of Pharmaceutical Information

1. Journals and bulletins
   - *Journal of the American Pharmaceutical Association*
   - *Journal of Pharmacy and Pharmacology*
   - *Drug and Cosmetic Industry*
   - *Pharmaceutical Journal*
2. Patents
3. Books
   - Pharmaceutical chemistry and pharmacy texts
   - "Remington's Practice of Pharmacy"
   - "U. S. Dispensatory"
   - "Merck Index"
   - "New and Nonofficial Remedies"
   - Official pharmacopoeias
   - "Martindale's Extra Pharmacopoeia"
4. Pamphlets and reports
   - Government reports
5. Technical information available from industrial firms
6. Trade association scientific papers
   - *Proceedings of the American Drug Manufacturers Association*
7. Theses
8. Personal communications

What is the best way to search these sources? The reference tools most useful in this particular stability problem are *Chemical Abstracts*, *Current List of Medical Literature*, and patent abstract services. Additional ones appear in Table IV.

Table IV. Reference Guides to Pharmaceutical Literature

1. *Chemical Abstracts* (1907–)
2. *Quarterly Cumulative Index Medicus (Q.C.I.M.)* (1927–)
3. *Current List of Medical Literature* (1942–)
4. Journal indexes
5. Indexes to books
6. Patent abstract services

Chemical Abstracts

Chemical Abstracts is the most comprehensive indexing and abstracting service, and by far the most useful for literature searches on pharmaceutical problems. Its abstract section on "Pharmaceuticals, Cosmetics, and Perfumes" is most pertinent. In the past few years, there has been greater specificity in the indexing of pharmaceutical articles in the subject indexes of *Chemical Abstracts*. Usually only general entries are made under such headings as "Stability," "Pharmaceuticals," etc.; articles on the stability of specific compounds are indexed under the compound—as "Vitamin C, stability of."

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Headings are generally terms or names in most common usage in this country; for this reason, subject headings—especially drug names—may change through the years. Less frequently used terms or names are included as cross references. Generic names are used in preference to trade names, although, if a trade name is much more familiar, articles may be indexed under the trade name. Chemical compounds are named and entered alphabetically; organic compounds are usually entered under the "parent compound," the names of the substituent radicals following alphabetically. In the case of ascorbic acid one needs only to look under "Vitamin C," but in many instances it may be necessary to look under three headings to locate the entries on a specific compound—the chemical name, the generic name, and the trade name.

To locate references pertinent to the stability of ascorbic acid one would search *Chemical Abstracts* under "Vitamin C." The subheading "stability of" or variations of this should be checked first. Other subheadings to be carefully checked are "oxidation of," "effect of," and "antioxidants for." It is worth while to skim other subheadings and their modifying phrases under "Vitamin C" for references indirectly related—for example, "compounds compatible with," "pharmaceuticals contg.," and "poly-vitamin soln. contg." appear in one annual index. Other pertinent references may be found under the main headings "Pharmaceuticals," "Oxidation," "Antioxidants," and "Reaction Kinetics."

Index headings pertinent to oxidation and other causes of instability are shown in Table V. These headings or variations of them are especially helpful when searching *Chemical Abstracts* but are, of course, applicable to other indexes. It is also worth while to check the type compound (alkaloid, amine, ketone, etc.) as well as the type preparation (tablet, ointment, lotion, etc.) under study. Obviously, such general headings are of most value if nothing can be found under the specific compound in question.

Table V. Index Headings Pertinent to Stability Problems

Stability
Reaction Kinetics, "Rate of Kinetics" under "Solution, Kinetics"
Oxidation, Antioxidants
Reduction, Oxidizing Agents
Hydrolysis, Heat of Hydrolysis, Lipolysis, Ionization
Racemization
Double Decomposition, Degradation, Reactivity, Decomposition, "Exchange" under "Bases"
Hydrogen-Ion Concentration, Acidity, Alkalinity, Isoelectric Point, Acid-Base Equilibrium
Solubility, Precipitation, Solubility Product, Solutions
Separation, "Separation" under "Emulsions, Miscibility"
Water, Absorption, Humidity, Vaporization, Evaporation
Temperature, Heat, Freezing, Refrigeration
Light, "Infrared" and "Ultraviolet" under "Light"
Radiation, Ultrasonics
Sterilization, Bactericidal Action or Bacteriostatic Action, Fungicides and Fungistats, "Preservation" under "Pharmaceuticals"

Current List of Medical Literature

To locate articles too recent to be indexed in *Chemical Abstracts*, one can examine the subject indexes of *Current List of Medical Literature*. This list is published monthly by the Armed Forces Medical Library and indexes articles of medical interest, but does not abstract articles. Its chief value is the fact that it is published monthly, as contrasted with the annual indexes to *Chemical Abstracts*. Cumulative indexes are published semiannually in June and December. Chemicals and drugs are usually indexed under their most common function or action, unless the compound is in wide usage. In that case, the drug or chemical name is a main heading. For example, articles on actinomycin are indexed under "Antibiotics," whereas articles on streptomycin are indexed under "Streptomycin." As in *Chemical Abstracts*, generic names are given preference to trade names. The modifying phrases in *Current List* are usually more general than those in *Chemical Abstracts*.

In searching *Current List*, time is gained by limiting the search to indexes issued since the last *Chemical Abstracts* subject index. Many of the references indexed under "Vitamin C" which seem pertinent to ascorbic acid stability are in journals that may not be readily available. Abstracts of those articles are usually published

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in *Chemical Abstracts*, as they are of chemical as well as medical interest. After selecting subject headings that seem pertinent and noting the authors of the references in *Current List*, the author indexes in the current year's issues of *Chemical Abstracts* will give the location of the abstract. The date of the issue containing the abstract roughly corresponds with the date of the listing in *Current List*.

Because of the abundance of pharmaceutical data included in the *Journal of the American Pharmaceutical Association (Scientific Edition)*, *Journal of Pharmacy and Pharmacology*, and *Drug and Cosmetic Industry*, it is a good idea to check recent issues. The abstracts sections of the two latter journals cover pharmaceutical articles, often foreign, which may contain helpful information.

Information on Patents

Recent patents can be covered best by using a patent abstract service. Although some journals—for example, *Drug & Cosmetic Industry*—list by title recent patent issues of pharmaceutical interest, no journal other than *Chemical Abstracts* indexes and abstracts patents of this type. Services, such as Invention, Inc., will prepare weekly abstracts of United States, British, and/or Canadian patents in specified fields of interest within 2 to 3 weeks of patent issue. Research Information Service prepares abstracts of German patent applications. In general, United States, British, Canadian, and German patents are the most helpful in studying pharmaceutical problems.

This company finds that the best way to handle patent data of potential help in stability problems is to make reference cards as the patents and patent abstracts are read. For example, if a patent describes an antioxidant for stabilizing ascorbic acid, cards are made to file under ascorbic acid and pharmaceutical stability. Reference cards from patents, brochures, technical data sheets, abstracts and proceedings of scientific meetings, some unpublished data, and about 200 journals, both foreign and domestic, are compiled by technical personnel in the Literature Department. Such screening by literature specialists is a partial solution to the ever-growing problem of keeping abreast of scientific developments.

When studying the stability of ascorbic acid, Literature Department reference cards are checked and thereby the several named sources covered at once. As the literature specialists prepare file cards only on information likely to be of interest to the company, these files are only supplemental to the published indexing services.

Other Sources

There are other indexing guides besides those shown in Table IV, both foreign and domestic, but none is known which covers only pharmacy. *Pharmaceutical Abstracts*, published from 1935 to 1947 by the American Pharmaceuticul Association, was discontinued because such a high percentage of the articles abstracted were also covered in *Chemical Abstracts*. For those who wish to find listings of indexing and abstracting services, volumes such as "Guide to Reference Books" by Constance M. Winchell, published in 1951 by the American Library Association, are available.

Ways to Improve Pharmaceutical Literature

Although many published reports may be found on the stability of ascorbic acid, few or no data are available on some other stability problems—because information is not indexed adequately from a pharmaceutical viewpoint or because such information has not been published. To overcome this situation, there is a need for more publications in better form, and more effective index systems to cover these publications.

To this end, certain improvements are essential to increase the value of the literature on stability and other pharmaceutical subjects.

More Data on Stability. Publication of more data on basic stability studies by those engaged in research and development is desirable, especially in industry. Perhaps 75 to 85% of such papers represent investigations carried on in academic institutions, although industrial grants support much of the work. That few publications of this type come from the pharmaceutical industries may perhaps be attributed to their understandable unwillingness to reveal aspects of the development of their products to competitors. Obviously, no company is going to describe how all of the problems in developing a complex product were overcome, and it is not even

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desirable from a literature viewpoint. Instead, it is desirable to publish more data on the stability of each ingredient in simple systems. Such publications might include the nature of reaction, rate of reaction, and factors and compounds affecting the reaction.

There is also a need for more publications on methods and conditions of stability testing, and comparisons of breakdown at exaggerated test conditions and "normal" conditions.

Better Presentation of Data. In preparing material for publication, special attention should be given to clear, concise presentation of experimental details. Such a minute detail as the source of an ingredient may alter the stability of a preparation. Moreover, the terse economy of charts and graphs makes it possible to interpret data more readily.

Descriptive Titles. Authors should select titles that describe the article, eliminating generalities where possible. All too often titles such as "Ascorbic Acid" make it necessary to refer to the original article to determine the scope of the paper. Index headings are often chosen from the information in the title of an article—so the more specific the title, the more specific the headings.

Better Indexing. Indexing of material should be adequate from a pharmaceutical viewpoint. One of the major reasons the literature on stability is so little used is that it is often difficult to find. Indexers must be made aware of the needs of academic and industrial investigators, so that better indexing of pharmaceutical data can be accomplished. Following are suggested ways of improving the indexing of journals and indexing services:

Data pertinent to stability should be indexed under the heading "stability" whenever possible. For example, an article on the deterioration of ascorbic acid solutions was indexed in *Chemical Abstracts* under "Vitamin C, deterioration of solns.," but not cross-indexed under "Vitamin C, stability, loss of."

More emphasis on the use of the word "Stability" as a main heading would be valuable in certain kinds of searching. For example, in making a literature search recently to find comparisons of drug breakdown under normal and exaggerated storage conditions, the searcher had no specific compounds in mind, but wanted only to learn whether any generalizations could be made by type of preparations or type of compound. Because most information on stability was indexed under specific compounds, it was impractical to do anything but a superficial search.

Pharmaceutical information included in articles in which the primary interest is in another field should be indexed. Such information cannot be located in a literature search unless it is indexed under the pharmaceutical aspect as well as headings related to the main aspect of the article. For instance, an article on the pharmacology of a new drug which includes compatibility and stability data should be indexed under "compatibilities" and "stability of" as well as "pharmacology of."

The Special Libraries Association has already recognized that existing services are not adequate from a pharmaceutical viewpoint. To help meet this deficiency it is planning to publish a weekly abstract bulletin, giving particular attention to such items as formulations and stability, especially when they appear in articles devoted to other basic interests. Articles from about 200 journals of medical, chemical, and pharmaceutical interest will be abstracted. It has not yet been decided whether the bulletin will be indexed.

Dissertations. Dissertations are a source of information not fully utilized. Although complete theses have not been available generally, scientific papers based on work carried out as part of graduate pharmacy programs are frequently published in the *Journal of the American Pharmaceutical Association.* However, to ensure the widest use of dissertations, a central listing of all titles and abstracts, and copies available for use, is desirable.

"Doctoral Dissertations Accepted by American Universities," published annually, contains a listing of titles, but apparently does not include dissertations from pharmacy schools and colleges. *Dissertation Abstracts* has been created recently to publish periodically abstracts of doctoral dissertations, title listings, and title and author indexes. Copies of the dissertations are available from University Microfilms, Ann Arbor, Mich. Since participation of the universities granting degrees is voluntary, cooperation is essential if all dissertations are to be available. Hopefully, pharmacy schools and colleges will cooperate, so that theses including information on stability of medicinal agents and other pharmaceutical problems may be freely available.

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Another possible reference is "Faculties, Publications, and Doctoral Theses in Chemistry and Chemical Engineering at United States Universities," printed by the Special Publications Department of the AMERICAN CHEMICAL SOCIETY. Only one issue, the 1953 edition, has been published to date, and frequency of publication has not been established. Current publications and interests of professors are listed under the name of the faculty member, which in turn is found under the alphabetical list of colleges and universities granting doctoral degrees in chemistry and chemical engineering. One will find it most useful if he knows that work is being done in a given field in a certain university or by a given professor.

Translations. The translation of foreign publications is often a deterrent in a literature review. To reduce the cost of translations, the Special Libraries Association has set up a pool to make available translations of articles from all languages, except Russian, at a nominal fee. This SLA Translations Pool is seeking translations of scientific articles from government agencies, technical societies, universities, and industries. The National Science Foundation has recently established a center for holding and photoduplicating scientific translations, with special emphasis on Russian. In Great Britain, the Aslib "Index of Translations in the British Commonwealth" serves the same purpose. Further information on these two domestic translation pools may be obtained by writing:

SLA Translations Pool
John Crerar Library
86 East Randolph St.
Chicago 1, Ill.

Scientific Translation Center
Science Division
Library of Congress
Washington, D. C.

Conclusions

A critical review of the literature on each ingredient is of great value in solving pharmaceutical formulation problems.

The most useful literature tool is *Chemical Abstracts*, because of its comprehensive coverage of patents, as well as pharmaceutical, chemical, pharmacological, and medical journals.

A literature scientist who combines familiarity with the literature with experience in pharmaceutical work can make the search more productive because of his understanding of the relatively obscure titles under which pertinent information is indexed and his knowledge of journals in which the stability information is included as a minor interest, and which would otherwise escape indexing.

The laboratory scientist needs to enlarge the literature by reporting more data derived from basic stability studies. Including the word "stability" in the title would make it more likely to be found in "index services" such as *Chemical Abstracts*.

Emphasis on the word "stability" both as a main heading and subheading in indexing is desirable.

Because theses from pharmacy schools supply much useful information, they should be submitted to *Dissertation Abstracts* to make them generally available.

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Instrumentation Applied to the Biological Sciences

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Techniques of indirect measurement, made possible by the vacuum tube, have led to many refinements and innovations in methods of measuring physiological responses in the living organism. These improvements have resulted not from the invention of new instruments, but through their application to measurement of biological phenomena. The older direct methods of measurement, which required relatively simple equipment, not infrequently produced disturbing influences on the organ systems involved, and were slow in response and limited in sensitivity. The newer procedures overcome many of these limitations, but with a sacrifice of simplicity. Development of newer techniques has required close cooperation between the biologist and the instrumentation specialist. The tying together of two widely separated fields of activity is a further complication in the problem of exchange of scientific information.

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Scientific progress in practically every field of investigation is directly traceable to the development and use of a wide variety of measuring instruments. The field of biology is no exception, yet the need for cooperation and better exchange of information is probably most acute between the sciences of instrumentation and biology.

Biology and instrumentation represent two highly skilled but seemingly unrelated fields. Biology, as defined, means the science of life or living organisms. Instrumentation, as used here, means the development and application of measuring devices which respond quantitatively to some physical property of a situation and give an output which depends on this property.

Although one field deals with the animate, the other with the inanimate, their dependence is evident if we analyze one of the simplest measurements that can be performed—counting a total number. In this instance, the object whose property is being measured is treated as a discrete entity, as when the hematologist counts red or white cells. The microscope and the graduated slide are instruments that permit him to make this measurement. More recently, a television eye and a high speed counter have replaced the technician, performing the operation in a matter of seconds. Sometimes the physical property is continuous, like changes in body temperature, blood flow, and blood pressure, bioelectric potentials produced by the brain, heart, and many other organs.

When man first started to examine the mechanism of life, he had to school himself along the lines of phenomenologic inductive approach, as he did not know what factors were involved or how to measure them. Lord Kelvin's famous words aptly describe the situation at that time: One's knowledge of a subject is of a poor kind indeed, unless one knows how to measure quantitatively the factors involved.

The consequence of this now famous statement is evident when we examine the rapid progress that was made in biology immediately following the introduction of biochemistry with its science of quantitative measurements. Today more is known about complicated chemical structures and chemical reactions within the body than about relatively simple physical processes.

On the first consideration it would appear that simple physical processes associated with animate matter would lend themselves readily to measurement. In-

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deed, as far back as 1600, Harvey, the father of circulatory physiology, started making systematic measurements in an attempt to correlate biological phenomena with physical laws. He was the first to demonstrate the circulation of blood, yet today, 300 years later, there is still no completely satisfactory method for measuring the blood flow in the intact living system. This research has lagged because in some instances it has been difficult to define the exact physical magnitudes involved, while in others the available principles or methods of measurement could not be applied without seriously influencing the system or the phenomenon itself.

Instrumentation as a Science

For a long time it was the responsibility of the scientist to develop and construct his own equipment, relying usually on the skill and ingenuity of a glassblower or a machinist. Today the ever-increasing emphasis on greater speed and sensitivity calls for more advanced physical methods of measurement, and the investigator, although a specialist in the phenomenon he wishes to measure, frequently cannot hope to attain the same degree of proficiency in building his measuring equipment, and even if he were proficient in the mechanical, electrical, and optical principles that enter into the design of an efficient instrument, he could not take the time from his research to devote to instrumentation.

Condon drew attention to this point in a speech before the Instrument Society of America when he said, "Prior to this century an analysis of the experimentalist's activity might have shown that the bulk of his time was spent in getting ideas and in analyzing the data of his subsequent experiments, while a minimum of time was spent in the construction of instruments. In the present period, too often the scientific situation is such that the bulk of his time has to be spent in devising and constructing his instruments."

If the investigator of today devotes any appreciable amount of time to instruments, he quickly realizes that he is actually dividing his efforts between two sciences, his own and instrumentation. This growing appreciation of instrumentation as a distinct science has taken place only within the last decade, and has come through the realization that the problems met in designing various kinds of instruments have a great deal in common. Recognition of this fact is exemplified by the formation of the Instrument Society of America, and the establishment at the National Bureau of Standards of a division of basic instrumentation devoted to the study of the basic problems of instrumentation (including mechanical, optical, electrical, and electronic) in all the physical sciences.

To the uninitiated it would seem that the instruments used are so various as not to have much in common. If this were so, there would be no general basis to the science of instrumentation. That it is not so is evident from the fact that two instruments, designed, built, and used for entirely unrelated purposes, will operate on exactly the same basic principle. For example, both the biologist and the engineer make use of the thermocouple for the measurement of temperature: one to measure body temperature, the other to measure furnace temperature. The instruments used are different in appearance but the principle employed is the same—namely, that two dissimilar metals, suitably joined, will generate a voltage that can be related to temperature.

Although the principle may be the same, the application will dictate how it shall be used. If the problem called for temperature measurements of venous blood, it would be necessary to make the sensing element very small, perhaps mount it inside a fine hypodermic needle. On the other hand, the engineer's concern may not be so much with the shape and size of the element, but rather with whether the metals withstand the temperature they may encounter. To develop either element requires a knowledge of both the principles of temperature measurement and the manner in which they are to be used.

This example also serves to illustrate a logical approach to analyzing many of our complex instruments. Usually only one part of the instrument has any bearing on the phenomena being measured and that is the sensing element, such as the thermocouple in the above example. The design of the intermediate and usually the greater and more complex part of the instrument, such as the amplifier, voltage stabilizers, and reference potentials, depends solely on the output of the sensing element, not at all on the physical quantity to be measured, and will be the same no

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matter in what branch of science it is to be applied. The last part of the instrument depends only on the use to be made of the data the instrument provides, such as in indicating, recording, or controlling.

The sensing element, or transducer, usually determines the usefulness of the instrument, and performs the function of translating one physical property into another. In measurements, the attempt is made to effect the translation so that it is evident to the sense of sight, which has the greatest sensitivity and resolving power. For example, although we can sense heat or cold, we can detect small difference in temperature only by observing the change in length of a mercury column in a thermometer. In the case of the thermocouple we perform an indirect measurement; the temperature change is first translated into a voltage, then magnified, and finally transformed into a suitable form for observation.

Electronics

Of late the emphasis has been more on transducers whose output is related to some electrical property such as voltage, resistance, capacity, or inductance. This permits the bulk of the instrument to be placed at some distance from the transducer, and through the use of electronics it is possible to attain almost any degree of speed and sensitivity commensurate with the transducer, and to perform such operations as multiplication, integration, differentiation, and many others.

Electronics has also made it possible to apply many of the discoveries that were made long ago but remained in a state of academic interest. For example, in 1880 the brothers Curie observed that when certain crystals were subjected to pressure or tension electric charges were developed on definite crystal surfaces. The piezoelectric effect is now used in microphones, accelerometers, pressure gages, and vibration pickups. Electronics has also stimulated study of other materials, and today the same effect can be induced in certain types of ceramics that do not exhibit this phenomenon naturally.

In biology, the fact that a principle of measurement is available does not guarantee that the measurement can be performed on a living system.

The problem of measuring blood flow, which was mentioned earlier, is exceedingly important whenever studies are undertaken on circulation, circulatory diseases, or the effect of drugs on circulation. There are many principles available for the measurement of liquid flow in pipes and tubes. Without exception, all of these have been applied and new ones have been devised by workers in the field. However, every method used so far has certain inherent disadvantages and the choice depends more or less on the problem at hand and the liberties one can take with the system being measured. Thus, if the vessel is accessible and can be cut, the blood can be by-passed through a flowmeter, such as a rotameter, and the flow read directly. There are also methods for measuring flow in the intact vessel; the first one was devised by Rein in Germany. The measurement is effected by placing two fine thermocouples on the vessel about 1 cm. apart and heating the vessel slightly in proximity to one thermocouple. Movement of the blood will produce a temperature gradient across the two points which can be related to the rate of flow.

However, none of these methods can be used to measure instantaneous flow, since the response time is slow. To measure pulsating flow an electromagnetic flowmeter is generally used. Actually the instrument measures the velocity of flow in a short length of tubing of fixed diameter inserted in the vessel, and the readings are then translated into flow. The principle itself is rather unique. Two small, nonpolarizable electrodes are mounted diametrically opposite each other in the tubing. A strong magnetic field is made to traverse the tube, and as the blood moves through this field a minute voltage is generated in that cross-sectional segment of blood that is perpendicular to the magnetic field. The resultant voltage is then amplified and recorded.

More recently a method was developed at the National Bureau of Standards for measuring the flow of liquids in pipes by measuring the difference in the velocity of propagation of ultrasonic sound with, and against, the direction of flow. It has been suggested that this technique may be used for measuring blood flow. If it can be applied, the method may have some added advantages, but like the others, it is basically a velocity measurement and spontaneous changes in vessel diameter ruin the quantitative accuracy. So far there is no direct physical method which does not

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require a surgical procedure, or which will permit repeated readings to be made in any size of vessel, in any part of the body under normal conditions.

Special Applications

Frequently, neither the biologist nor the instrumentation specialist has a well defined notion of the underlying factors of the phenomena which are amenable to measurement. An illustration is a sequence of developments that took place in the author's laboratory.

During the course of work on vitamins the question arose, whether the lack of a specific vitamin would inhibit the ability of an animal to perform a prescribed task. The rat was the animal of choice and the task was swimming, as it was possible to elicit a fair degree of cooperation from the animal without recourse to any secondary stimuli. The first measurement was merely of the length of time the animal could swim with a given fixed weight. In such a procedure, the end point is difficult to define because the rats are clever, and as they attempt to rest or swim under water one may overestimate their ability and inadvertently lose valuable animals. To overcome these difficulties and provide greater versatility in application and reading, an apparatus was built that resembled a heavy-duty balance. The animal was suspended from one arm of this balance in a special harness, and the other arm supported a mechanism which automatically adjusted a counterweight depending on the animal's efforts. A continuous record of the weight changes was made during the course of the experiment. The results were encouraging, especially as it was possible to rate the individual animals on the basis of their gradually diminishing effort, eliminating the need for continuing the experiment to complete exhaustion. However, the system had a great deal of inertia and it was felt that a better insight would be had into the manner in which the animal behaved if rapid changes in effort could be sensed, as lack of coordination might bear some relation to the onset of fatigue.

At about that time efforts were diverted to a seemingly unrelated problem—viz., development of a rapid-reading device for an analytical balance. Although differing in application, the problem was basically the same—namely, measuring sudden changes in weight, taking into account the effect of inertia on the deflection of the balance. To satisfy every possible set of circumstances, it became evident that it was necessary to solve the differential equation decribing the motion of a balance. To be practical, this calculation had to be performed as soon as the balance gave any indication of motion, so that the information could be transmitted to the indicator or controller. This was finally accomplished by designing a suitable electronic analog computer.

With this new technique, an instrument could be designed which would not only determine the total energy expended by the swimming animal, but also follow the effort associated with each individual swimming stroke.

In biological instrumentation examples such as the above are the rule rather than the exception. However, instrumentation can also serve in many other capacities, not the least of which is relieving the investigator of routine chores, thereby allowing him more time for designing new experiments and testing new theories. The biologist is dealing with an exceedingly complex system and until he can account for all the variables and constants that he now must approximate, he is working with averages necessitating numerous observations. Even at this early stage of development, scientific instruments have much to offer in terms of automatic features, reliability, and reproducibility as contrasted to the errors inherent in human observation.

Obviously the situation can be solved only through cooperative effort. However, such cooperative effort is impeded not only by the normal restraints of time, money, and availability, but also by lack of understanding between the workers in the various fields and indeed by the lack of contact between them. At the present time, as with all new ventures, we are going through a period of adjustment. The situation is somewhat chaotic, particularly in the difficulty of finding all the latest information on new measuring techniques.

Publication

Today only one journal in the United States is devoted solely to the field of instrumentation, and the funds available to it from affiliated societies are wholly in-

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commensurate with the activity in the field. However, certain journals such as the *Review of Scientific Instruments* and the *Journal of Laboratory and Clinical Medicine* are devoting sections to methods, techniques, and physical instruments for the biologist. Much valuable scientific information is being disseminated through publications, bulletins, and house organs of manufacturers; they contain bibliographies, special hints and unusual uses, and other guides of value in the application of the instrument to special problems. On the other hand, reports of physicists, electronic specialists, and other nonbiologists who have been interested in the application of their findings to biology are scattered throughout the literature in various branches of physics, electronics, and biology. In an effort to provide a common meeting ground for the exchange of just such information, the Institute of Radio Engineers recently formed a professional group on medical electronics and at present this group is providing the only organized activity of its kind in this vital field.

Biophysics

To bridge the gap between physics and biology, a new science is gradually coming into its own—biophysics. At the present time this science does not have an established domain nor a generally accepted curriculum of prescribed education, because physics borders on practically every field of biological specialization. The biophysicist may be expected to be better versed in instrumentation, but it is no more his intent to devise his own instruments than it would be for a biochemist or a physical chemist. However, if the science of biophysics can find expression through its own journal, it may provide a more logical central repository for information on instrumentation than any other branch of biology.

Communication Problem

At the moment, there is perhaps no real solution available and all that one can do is to explore the nature and the magnitude of the communications problem. This problem is vast, and of a somewhat different nature than that of communications within a single science or specialty. More technical bulletins, papers, journals, etc., are not an adequate solution. After all, communication is dependent, in the last analysis, on the interest of the recipient and on his ability to understand. The biologist interested in blood flow, for example, has no interest in, nor understanding of, the necessary instrumentation and has neither time nor inclination to read instrumentation journals, nor would they help him much if he did, as the language and approach are quite foreign to his field.

The problem of communication between the biologist and the instrumentation worker is one of increasing importance and growing priority. Lack of means of bringing all the scattered information together will defeat the ultimate purpose of scientific writing, as was so well put by MacDonald, who said, "By the interchange of information today's work can begin where yesterday's ended; one need not do again today what was well done yesterday."

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Abstract and Index Services in the Pharmaceutical Field

WINIFRED SEWELL, ANNE McCANN, and IRENE KELLY

Library, Squibb Institute for Medical Research, E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corp., New Brunswick, N. J.

Existing abstract services of great importance to the pharmaceutical industry are *Chemical Abstracts* and the *Current L of Medical Literature*. Both save many hours that would otherwise have to be spent by an individual organization, but there is room for improvement in the length of time between the appearance of the journal and the appearance of abstracts or titles from it, coverage of periodicals of interest to the pharmaceutical industry and of pharmaceutical aspects of the articles indexed or abstracted, indexing of items of pharmaceutical importance, and the time required for indexing in the individual library. *British Abstracts of Medical Science Chemisches Zentralblatt,* and *Quarterly Cumulative Index Medicus* are also helpful.

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In the highly competitive pharmaceutical field awareness of all published work is essential. Librarians need to be able to provide their clients with chemical, pharmacological, toxicological, or clinical publications on any drug as soon as they appear and at any subsequent time. To meet this need a great many libraries in pharmaceutical companies and colleges of pharmacy provide one or more special services. They may circulate tables of contents, prepare and distribute abstracts, or maintain an index of current periodical articles. Yet each kind of service is available from one or more of the existing publications which index and abstract pharmaceutical material. Why, then, do individual libraries find it necessary to go into the expensive business of duplicating or supplementing work that is being done elsewhere? What do the existing publications lack? To answer that question is the purpose of this paper.

Services which compile information from published sources may be grouped broadly into "news" and "reference" types. The news type would include compilations that keep the individual scientist informed of current developments without special concern for his being able to locate the information when it is needed later—for instance, *F-D-C Reports* and *Drug Trade News*. The reference type would be defined as publications that systematically provide for finding information retrospectively. If it appears promptly enough, the reference type of publication may also be a source of news for the scientist.

There are a number of lists which include both broad and specialized abstracting and indexing services of pharmaceutical interest *(3–8, 12)*. They should provide a basis for extensive studies. It has been necessary to limit the present paper to currently published reference services useful in broad areas of the pharmaceutical field.

List of Services Studied

Biological Abstracts (BA), Union of American Biological Societies, Philadelphia, 1926 to date. Monthly. Annual subscription, $50.

British Abstracts of Medical Sciences (BAMS), London, January 1954 to date. Monthly. Annual subscription, $30.

Chemical Abstracts (CA), AMERICAN CHEMICAL SOCIETY, Easton, Pa., 1907 to date. Semimonthly. Annual subscription, $15 to members of the Society, $60 to nonmembers (1955). New rates will be in effect in 1956.

In A Key to PHARMACEUTICAL AND MEDICINAL CHEMISTRY LITERATURE; Advances in Chemistry; American Chemical Society: Washington, DC, 1956.

Chemisches Zentralblatt (CZ), Akademie Verlag, Berlin, and Verlag Chemie, Weinheim, 1830 to date. Weekly. Annual subscription, $76.
Current List of Medical Literature (CLML), Armed Forces Medical Library, Washington, D. C., 1941 to date. Monthly. Annual subscription, $12.
Excerpta Medica (EM), Amsterdam, 1947 to date. Monthly. Published in 16 sections. Annual subscription, $260; price per section varies, $10 to $45 a year.
Quarterly Cumulative Index Medicus (QCIM), American Medical Association, Chicago, 1927 to date. Cumulative volume published semiannually. Annual subscription, $20.

Since the discontinuation of the *Squibb Abstract Bulletin* in 1952, the Squibb Library staff has been examining other publications to see whether they can replace the bulletin or if supplementary library indexing or abstracting is required. Consequently the studies here reported have been made over a 2-year period and are not always strictly comparable. In general, the following points have been investigated for each publication: (1) interval between publication of the original article and its appearance in the abstracting or indexing service; (2) interval between publication of the original article and its coverage by the indexes of the service; (3) coverage of periodicals of interest in the pharmaceutical field; (4) coverage of individual articles of interest in the pharmaceutical field; and (5) adequacy or inadequacy of the indexing from the pharmaceutical point of view.

For many parts of this study a basic list of 16 journals has been used. British, French, German, and American journals were selected and the variety of subject fields represented is believed to be typical of the basic interests of the pharmaceutical research scientist and clinical worker.

Pharmacology (4)	*Journal of Pharmacology and Experimental Therapeutics; Journal of Pharmacy and Pharmacology; Archives internationales de pharmacodynamie et de therapie; Archiv für experimentelle Pathologie und Pharmakologie*
Biochemistry (2)	*Journal of Biological Chemistry; Comptes rendus des séances de la société de biologie*
General science (1)	*Science*
Medical science (1)	*American Journal of the Medical Sciences*
Clinical medicine (including specialties) (8)	*Journal of the American Medical Association; American Journal of Medicine; Archives of Internal Medicine; American Journal of Obstetrics and Gynecology; Presse médicale; Deutsche medizinische Wochenschrift; Schweizerische medizinische Wochenschrift; British Medical Journal*

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Interval between Publication and Abstracting

In this discussion the date on the journal is used for original articles rather than the actual date of issuance. The resulting time lags between primary publication and abstracting or indexing may be somewhat large, but they cancel out in comparisons.

Current List of Medical Literature is more prompt with respect to subject indexing than any other publication being considered. Not only is an article indexed by subject and author in the same monthly issue in which it is listed, but a cumulated subject and author index appears semiannually. The July–December 1953 issue was received in the Squibb library early in June 1954, and the January–June 1954 index was received early in September. In the July 1954 issue (received July 1, 1954), 40 (3%) of the journals indexed were dated less than 3 months previously, 16% less than 4 months previously, and 48% less than 6 months before. Of the journals indexed, 211 (18%) were dated December 1953.

A check of the 16 selected journals shows that the July 1954 issue of *Current List of Medical Literature* covered April issues for the *British Medical Journal*, *Journal of the American Medical Association*, and *Archives of Internal Medicine*. March issues of all of the other seven English-language journals were indexed, except for the *Journal of Biological Chemistry* (February 1954). The dates of the five foreign-language journals included are: *Presse médicale*, January 9–February 20, 1954; *Schweizerische medizinische Wochenschrift*, January 2–30, 1954; *Deutsche medizinische Wochenschrift*, January 15, 1954; *Archives internationales de pharmacodynamie et de thérapie*, October 15, 1953; and *Comptes rendus de la société de biolo-*

gie, August–October 1953. *Archiv für experimentelle Pathologie und Pharmakologie* was not represented. In short, 9 of 16 important journals were dated less than 4 months previously.

The July–December 1951 *Quarterly Cumulative Index Medicus* was not received until August 10, 1953. Of the selected journals checked *(American Journal of the Medical Sciences, Journal of Pharmacology, Journal of the American Medical Association, Journal of Biological Chemistry,* and *Science)*, November 1951 issues of all were indexed by author and subject and even the December 29 *Journal of the American Medical Association* was included. The time lag between appearance of journal and of indexing in these instances was 19 to 20 months.

The proposed monthly subject index to *Chemical Abstracts* would immeasurably improve the reference usefulness of this very valuable publication. A survey of the coverage of the selected journals in 1951 revealed that abstracts of articles from January 1951 journals appeared fairly promptly for the *Journal of Biological Chemistry* (mostly by May 25 and all by September 25); *Journal of Pharmacology* (April 25 and May 25); *Journal of Pharmacy and Pharmacology* (June 10); *Archives internationales de pharmacodynamie* (mostly May 10, and 17 of 18 by August 10); and *Science* (February 25 to June 10). Some papers from *Archiv für experimentelle Pathologie und Pharmakologie* appeared in the October 25 *Chemical Abstracts; Comptes rendus de la société de biologie* had 31 of 60 papers abstracted between July 10 and November 10; *American Journal of the Medical Sciences* had 7 of 12 papers abstracted in the November 10 issue; and 3 of 10 papers from the *Archives of Internal Medicine* were abstracted in the June 10 issue. At the time of this work, the 1952 indexes were not available, although a subsequent check in some cases produced no added references. The other selected journals were so spottily covered that dates of abstracting would have little significance.

A count of every fourth column of the July 10, 1954, *Chemical Abstracts* (received July 28) showed 358 abstracts from 1954 journals and 346 from 1953 or earlier. Though this suggests an average interval between publication of article and of abstract of about 7 months, the "Organic Chemistry" section contained in the columns checked only one abstract of a 1954 paper, whereas there were 8 abstracts dated before 1953 and 31 for 1953. In the July 10, 1954, issue substantially all organic chemistry patents abstracted had been published between May and August 1953; there were four foreign-language patents from 1952. Among the 1952 abstracts was one on degradation of Aureomycin from the *Journal of the American Chemical Society (Chem. Abs.*, **48**, 7594a). It seems a shame that the librarian may have to wait until the fall of 1955 before locating it in the *Chemical Abstracts* subject index. The 1952 subject index was received in September 1953 and only half of the 1953 subject index had issued by August 1, 1954. This means that at present from 8 or 9 to 20 or 21 months must be added to the time lag for abstract issuance to obtain a figure for time between appearance of a journal and of the subject index covering abstracts from it. Author indexes appear in each issue of *Chemical Abstracts* and their annual cumulation is fairly prompt.

Biological Abstracts was found in an excellent survey done at Johns Hopkins *(2)* to have, for United States journals, an average interval between publication of article and publication of abstracts of 0.66 year with a range from 0.36 to 0.95 year for "author-abstracted" journals and an average interval of 0.9 year with a range from 0.63 to 1.66 years for "non-author-abstracted" periodicals. These figures agree closely with the study of lags between dates of journals on the selected list and publication of abstracts in *Biological Abstracts.* Though the surveyors seem reasonably well satisfied with this record, it is not fast enough for pharmaceutical libraries, particularly since the latest subject index, for 1950, was received in September 1953. Here 33 to 45 months must be added to the article-abstract interval to obtain time between article publication and indexing in *Biological Abstracts.* Monthly and annual author indexes are being received promptly.

Intervals between article and abstract or indexing publication for *Excerpta Medica* vary with the different sections. It is sometimes difficult to determine when a given article was abstracted, because one cannot be sure in which section or sections it has been included. The *American Journal of the Medical Sciences* and *Journal of Pharmacology* for July 1951 have been checked in all sections; for the 23 abstracts located 18 appeared in the first half of 1952, mostly in April or May; one

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appeared in July, two in August, and one in December of 1952, and one in May of 1953. This suggests a time lag of from 9 to 12 months, occasionally ranging to almost 2 years. The April 1954 issue of the new Section XVI (Cancer) abstracted only four articles for 1954 against 248 for 1953 and 26 for 1952. Though the month of the periodicals abstracted was not indicated, the issue number was given. The highest percentages of 1953 journals were from issues numbered 3 or 4, a fact which indicates that many March and April journals were covered.

Subject indexes for 8 of the 15 sections published throughout 1953 had been received before July 1954; one of the others had been indexed through June 1953; four through December 1952; Section III (Endocrinology) through December 1951; and Section II (Physiology, Biochemistry, and Pharmacology) through June 1951. Time lag between journal publication and indexing might therefore be anywhere from 9 months to 5 years, with the average interval probably closer to a year. Author indexes are published monthly.

Chemisches Zentralblatt appears to restrict its coverage closely to chemical journals, so that abstracts of articles from many of the periodicals on the selected list were found rarely or not at all. Of 20 articles from the February 1953 *Journal of Biological Chemistry* checked through the June 23, 1954, author index, five appeared in September, seven in November, three in December 1953, one in January 1954, and four not at all. The "Pharmazie" and "Pharmakologie" sections of the June 23, 1954, issue carried only one abstract from a 1954 journal (February), 38 from 1953 (of which 18 were published in September and October), 24 from 1952, and one from 1951. The first third of the "Präparative organische Chemie (Naturstoffe)" section, however, contains six 1954 abstracts along with fourteen from 1953 and seven published earlier. This indicates an average lag of 9 or 10 months between journal and abstract publication. The most recent subject index received in the Squibb library is for 1951; the second half arrived in February 1954. The overall indexing lag is therefore considerably greater than for *Chemical Abstracts*. Though each issue includes an author index, the cumulative author index for 1953 was not received until July 15, 1954.

The new *British Abstracts of Medical Sciences* was started in January 1954, with a considerable interval between primary article and abstract publication. Of the 996 items in the July 1954 issue (received August 5), 754 were from 1953 periodicals, 203 from 1954, and 39 from 1952. Though month of issue was not given, it is obvious that a large portion of this material is more than 7 months old when received. As no indexes have appeared, coverage of specific issues of journals could not be checked.

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Coverage of Periodicals of Pharmaceutical Interest

To study coverage of journals of pharmaceutical interest available lists of periodicals indexed or abstracted were checked against "Union List of Periodicals in Pharmaceutical Libraries" *(11)*. Twenty-three of the 25 industrial libraries whose holdings are listed are in the United States and the other two are in Canada. Though the list is naturally weighted in favor of English-language and North American journals and colleges of pharmacy are not represented, it is a working guide to journals actually being used in the pharmaceutical field. All periodicals known not to be current were eliminated and every fifth page of the "Union List" was checked against the following:

List of Periodicals Abstracted by *Chemical Abstracts* with Key to Library Files and Other Information (*Chemical Abstracts*, Columbus, Ohio, 1951) [Also published with 1951 indexes].

Journals Abstracted in *Biological Abstracts*. *Biological Abstracts*, **28**, iii–xxix (May 1954).

List of Journals Indexed. *Current List of Medical Literature*, Cumulated Subject and Author Indexes, **24**, i–xii (July–December 1953).

List of Journals Indexed. *Quarterly Cumulative Index Medicus*, **51**, 65–78 (January–June 1952).

United Nations, World Health Organization and Education, Scientific and Cultural Organization. World Medical Periodicals (Paris, WHO and UNESCO, 1953) [Checked for items covered in *Excerpta Medica* only].

Table I. Overlapping of Journal Coverage by Abstracting and Indexing Publications

Numbers in columns indicate the number of journals indexed in the publication at the top of the column and in all other publications which have the same number in the same cross column.

Only 1 service	*CA*	*BA*	*QCIM*	*CLML*	*EM*	*Total*
(43)	33					33
		3				3
			4			4
				3		3
2 services	24	24				24
(38)	2		2			2
	2			2		2
	4				4	4
		1		1		1
			2	2		2
			2		2	2
				1	1	1
3 services	2	2		2		2
(20)	3	3			3	3
	3		3	3		3
	1		1		1	1
	5			5	5	5
		4	4	4		4
			2	2	2	2
4 services	1	1	1	1		1
(26)	2	2	2		2	2
	5	5		5	5	5
	16		16	16	16	16
		2	2	2	2	2
5 services	39	39	39	39	39	39
(39)	142	86	80	88	82	166
			Not covered in any list checked			58
						224

Of the 224 current journals on the 38 pages of "Union List" checked, 39 were included in all five of the above lists, 26 in four, 20 in three, 38 in two, 43 in one, and 58 in none. A breakdown by individual services is given in Table I. The 58 periodicals not on any of the services' lists are classified as follows:

Miscellaneous county medical society or medical clinic journals	11	South American journals (2 medical and 2 pharmacy)	4
National, state, or regional pharmacy journals	10	Infrequently issued society proceedings	2
House organs	6	Regional hospital journals	1
Current scientific news organs	4	Pharmaceutical education journals	1
Abstracting journals	4	Chemical journals	1
Veterinary journals	4	Miscellaneous journals	10

The miscellaneous 10 were business, statistical, or library journals which one would not expect to find. In spite of the fact that these 58 journals could not be claimed to represent glaring omissions, we all know isolated cases of the appearance of important papers in obscure journals.

Coverage of Individual Articles

All signed articles from the tables of contents of medical and medical science periodicals checked were included in the *Current List of Medical Literature*. The nonphysiological items from *Science* were, of course, omitted. The *Current List of Medical Literature* also includes obituaries and some editorial, legislative, and organizational material. No letters or abstracts of meeting papers were found.

Quarterly Cumulative Index Medicus also included all signed articles from the medical journals checked (July 1951 issues of *American Journal of the Medical Sciences* and *Journal of Pharmacology* and July 7, 1951, *Journal of the American Medical Association*). The only special sections covered, however, were obituaries

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and the more important announcements from the American Medical Association Councils. The inclusion of signed articles from the July 6, 1951, and November 30, 1951, issues of *Science* was selective. A veterinary article on treatment of dairy cattle with cortisone and ACTH was not there. Neither were items from the "Comments and Communications" section, although some of them had physiological implications. No abstracts of meeting papers were found. The basis for selection by the *Quarterly Cumulative Index Medicus* of items from the July 1951 *Journal of Biological Chemistry* is hard to trace. Generally physiological articles were included and those on syntheses of chemicals were not, even though the syntheses were biological. But why was an article on the metabolism of hypoxanthine desoxyriboside in animal tissues left out when one on the metabolism of Furacin by incubation with mammalian tissues was taken? Twenty-one of 49 articles in this issue were indexed.

Excerpta Medica appears to have rather complete coverage of medical and pharmacological journals. The herculean task of checking all author indexes of every section up to date was accomplished for two journals, the *Journal of Pharmacology* and *American Journal of the Medical Sciences*, both for July 1951. Three of the 26 papers were not found, two from the *Journal of Pharmacology* (on lactones in treatment of experimental trypanosomiasis and the metabolism of labeled salicylic acid), and one from the *American Journal of the Medical Sciences* (on a diagnostic pulmonary artery pulse pressure counter).

Chemisches Zentralblatt was checked through June 23, 1954, for inclusion of articles in 1953 issues of a few journals. The proportion of articles found to those checked was: February 1953, *Journal of Biological Chemistry*, 16 of 20; January 2, 1953, *Science*, none (an abstract from a later issue was noticed); January 1, 1953, *Archives internationales de pharmacodynamie*, 5 of 21; Volume 217, No. 1 (1953) of *Archiv für experimentelle Pathologie und Pharmakologie*, one of 10; and January 1953 *Journal of Pharmacology*, none. In three cases, although the articles being checked did not appear, a similar one by the same author but from another journal had been indexed.

When the 16 journals on the selected list were checked against the *Chemical Abstracts* index, it was found that, like the other services, it does not include references to abstracts of meeting papers. Otherwise all papers from the January 1951 issues of English-language pharmacology and biochemistry journals were in the 1951 index. The only omission from *Archives internationales de pharmacodynamie* was a paper titled "Autonomic innervation of the udder in sheep and cows," scarcely something one would expect to find in *Chemical Abstracts*. Volume 212 of *Archiv für experimentelle Pathologie und Pharmakologie* for late 1950 and early 1951 was more spottily covered; and about half the papers in the January 1951 *Comptes rendus de la société de biologie* were abstracted. Six of 11 papers from the January 5, 1951, *Science* were found. Those omitted were in the fields of botany, biology, geology, and radiology. For the January *American Journal of the Medical Sciences* 7 of 12 articles were abstracted. A study on coexistence of cirrhosis of the liver and glomerulonephritis was omitted, while papers on liver biopsy and localized paroxysmal hyperhidrosis were included.

Though all the clinical medicine journals on the selected list are on the "List of Periodicals Abstracted in *Chemical Abstracts*," only two of the January 1951 issues from this group were represented in the 1951 *Chemical Abstracts* index. Of 11 papers in the January 5, 1951, *Deutsche medizinische Wochenschrift*, a single one (on tetany and the gonads) was noted. For the *Archives of Internal Medicine* the pattern of selection for the three papers found was hard to detect. Papers abstracted included those on diagnostic and therapeutic use of radioactive iodine, while one of the seven omitted was on diabetes precipitated by drugs. A review on gastric changes in pernicious anemia was published in two parts; the section subheaded "Physiology" was indexed, but that on "Pathology" was not. Nor were the omissions from the six other clinical journals readily explainable. In the *British Medical Journal* an article entitled "Investigation of the Properties of Isopropyl Chloride" was not indexed. Similarly, "Raised Blood Pyruvic Acid Level in Diabetic Acidosis" was not included, though "Effect of Implantation of Tablets of Insulin on Normal and Alloxan-Diabetic Rabbits" by the same authors in *Lancet* [**260**, 143–6 (1951)] was abstracted April 10, 1951. "Oral Use of Cortisone Acetate," by E. W.

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Boland and N. E. Headley [*J. Am. Med. Assoc.*, **145**, 8–11 (Jan. 6, 1951)] was not abstracted, though Boland's review article on cortisone and ACTH published in *California Medicine* [**72**, 405–14 (1950)] was included. Among *American Journal of Obstetrics and Gynecology* papers disregarded were studies of the vasomotor properties of Methergine; hyperestrogenism and its therapy; postspinal anesthesia headaches; and radioactive iodine for hyperthyroidism.

The survey of *Biological Abstracts* directed by Bentley Glass of Johns Hopkins *(2)* indicates that its record for complete coverage of the journals included is poor, even though the articles are in the biological field. Percentages of articles not abstracted during the period 1947 to 1949 from some journals of pharmaceutical interest are: *Archives of Biochemistry*, 13.9%; *Circulation* (Volumes 1 and 2), 7%; *Journal of Investigative Dermatology*, 69.1%; and *Comptes rendus de la société de biologie*, 69.1%. The surveyors point out that in some cases errors in the index may have led to the belief that an article was not abstracted when it actually was, an observation which would apply equally to studies of other works. As they state, however, "an error in the index that prevents a searcher from finding the abstract of an article is essentially equivalent to the failure to abstract it."

In the present study, which was done before the Hopkins survey became available, selection of articles from January 1949 journals for *Biological Abstracts* was compared with that for the *Squibb Abstract Bulletin*. Most of the papers covered by the latter were also covered by *Biological Abstracts*. Seven of eight articles from the *Journal of Pharmacy and Pharmacology* which were included in the *Squibb Abstract Bulletin*, however, were not found in the 1949 *Biological Abstracts* index. Similarly, three articles from the *Journal of Pharmacology*, three from the *Journal of the American Medical Association*, two from the *British Medical Journal*, three from *Archives internationales de pharmacodynamie*, and one each from *Science* and *Journal of Biological Chemistry* were omitted by *Biological Abstracts* but included in the *Squibb Abstract Bulletin*, an average of about 10 items having been checked for each journal.

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Adequacy or Inadequacy of Indexing

As would be expected, the emphasis of the *Current List of Medical Literature* in its indexing does not always coincide with the point of view of a pharmaceutical house. Some time ago 40 articles were checked for indexing in Volume 21 of the *Current List of Medical Literature* (January–June 1952). Although there have been changes and improvement since then, the general practices discussed here appear to remain the same and should be kept in mind when using the earlier indexes. Some examples from the Volume 21 index are therefore used. In recent indexes items on therapy of tuberculosis with streptomycin are all under both "Tuberculosis" and "Streptomycin," an improvement over earlier indexes, in which one must check both places for complete coverage.

The *Current List of Medical Literature* indexes from the article itself rather than from the title. Because emphasis is placed on diseases and pathologic conditions, a drug that may appear to be relatively unimportant in an article is not always indexed. Though the insulin heading is used in the Volume 21 index, two papers were not found under it. They discuss the citric acid cycle in tissues of normal and diabetic rats and of alloxan-diabetic rats treated with insulin (**21**, 38358), and the effect of insulin hypoglycemia on alimentary hyperglycemia (**21**, 38364). An article (**21**, 38324) on the synthesis of radioactive fatty acids in vitro and its hormonal control is under "Hormones, effects," "Fatty acids, metabolism," and "Liver, metabolism" only, although the specific hormones, insulin, anterior pituitary growth hormone, and cortisone are all of pharmaceutical interest.

Inconvenience and occasional errors are caused by the frequent use of class headings for drugs rather than specific ones. An article (**21**, 37949) on the use of *N*-allylnormorphine (nalorphine) in methadone poisoning was under "Morphine, therapeutic use in methadon poisoning" without mention of nalorphine. Two other articles on nalorphine in Volume 21 were under "Morphine, derivatives." In Volume 24 (July–December 1953) nalorphine is more properly indexed under "Morphine, antagonists," but there are no cross references from "Normorphine, *N*-allyl-," "Allylnormorphine," "Nalorphine," or "*N*-Allylnormorphine."

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Throughout the index more cross references would be helpful. The Volume 24 index, for instance, carries a cross reference from "Testosterone" to "Androgens"; but, although articles on methylandrostenediol are found under "Androgens," there are no cross references from "Methylandrostenediol," "Androstenediol, methyl-," or any of 17 trade and generic names for the drug.

The chemist may wonder at the consistent use of "Coumarin" as a synonym for "Dicumarol" [3,3'-methylenebis (4-hydroxycoumarin)]. It also seems a little inconsistent to index isonicotinic acid hydrazide under "Nicotinic acid isomers" but to put nicotinaldehyde thiosemicarbazone under "Thiosemicarbazones" with subheadings for "β-pyridine aldehyde" or "nicotinaldehyde" interspersed among various subdivisions covering other thiosemicarbazones. There are no cross references from nicotinaldehyde or its parent. Incidentally, under nicotinic acid isomers, the subheading "therapy, tuberculosis" is frequently used without mentioning the hydrazide, although it seems likely that the hydrazide was used in all cases.

Like the *Current List of Medical Literature*, the *Quarterly Cumulative Index Medicus* indexes under diseases and pathologic conditions. But the difficulties in using its index are different. The *Quarterly Cumulative Index Medicus* uses cross references liberally, to the point where they interfere considerably with rapid reference work. In order to have a complete list of the Banthine references for July–December 1951, one must check under eight separate headings, such as "Colitis, ulcerative," "Peptic ulcer, therapy," and "Herpes zoster," totaling about 14 columns of fine print. For this effort, one comes up with 23 references. In the case of "Skin, diseases," only one reference was found in the 3½ columns referred to. The difficulty of repeating a citation under every heading to which it applies is obvious, but some sort of numerical reference for each item might save the user unnecessary effort.

Drug indexing is less specific in *Quarterly Cumulative Index Medicus* than in the *Current List of Medical Literature*. Whereas the *Current List* has a separate heading for Banthine, in *Quarterly Cumulative Index Medicus* curarizing agents, hypotensive drugs, and antibacterials as well as Banthine are intermixed under the heading "Ammonium compounds, quaternary ammonium compounds." The *Current List of Medical Literature* separates this conglomeration by using "see also" references from "Ammonium compounds" to "Antiseptics, quaternary ammonium" and to "Tetraethylammonium." No mention is made of the heading "Muscle relaxants," however, where hexamethonium compounds are found. Nor can they be found by checking "Hexamethonium." There is a cross reference to "Muscle relaxants" from "Methonium compounds."

In checking the *Quarterly Cumulative Index Medicus* the following omission of a secondary drug was discovered and it was subsequently found not to have been brought out in other services either. One of the cross references from "Methantheline" (Banthine) is to "Sweat glands, diseases," where one article mentioning Banthine is cited. A user would not recognize the article indexed there, "prantal (quaternary ammonium compound) in treatment of hyperhidrosis" [Nelson, L. M., *J. Invest. Dermatol.*, **17**, 207–8 (October 1951)] as one which also contains information on Banthine. Yet not only had two patients treated with Prantal been previously treated with Banthine, but four who failed to respond to Prantal were given Banthine, two being relieved. The same article is in Volume 21 of *Current List of Medical Literature*, where a cross reference from "Banthine" to "Parasympatholytics" is used and it appears under the subhead "therapeutic use, hyperhidrosis, prantal," again without mention of Banthine. It also appears in the January 1953 *Excerpta Medica*, Section XIII (item 107), in which a four-line abstract merely mentions number of patients, dosage, and side effects for Prantal, and states that results were uncertain; it was indexed under "Hyperhidrosis" but not under either drug, though "Banthine" occurs as a heading in this index. It was not found in the 1951–53 author indexes to *Chemical Abstracts*, nor in the 1951 author index to *Chemisches Zentralblatt*. *Biological Abstracts* has no subject index for that period.

The subject index to *Chemical Abstracts* is extremely useful, as a chemical approach pinpoints an individual drug in a way in which the indexes discussed thus far do not. All of 12 articles from the *Journal of Pharmacology*, *Journal of Pharmacy and Pharmacology*, and *Journal of Biological Chemistry* examined are adequately indexed by drug. For an article on pharmacology of analgesics in rats, *Chemical*

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Abstracts uses seven specific drug entries, though not the general heading "Analgesics." Because it has entries for the disease treated as well as for the drug used in therapeutic articles, it is unfortunate that there are so comparatively few such articles. Though *Chemical Abstracts* cross references were found to be good, there were none for methylandrostenediol from "Androgens" or any generic or trade name known to the two headings used in the 1952 subject index, "Androstenediol, methyl-" and "5-Androstene-3β, 17β-diol, 17α-methyl-".

Biological Abstracts lies somewhat closer than *Chemical Abstracts* to the medical indexes in its approach to drugs. An article on three new antihistaminic thenyl derivatives of β-dimethylaminoethylpyridine (*Biol. Abs.*, **23**, 15127), for instance, was indexed under "Histamine, antagonists, thenyl-ethylenediamine derivatives as," but not under "Thenyl, etc." or under such likely entries as "Pyridine, derivatives" or "Ethylenediamine, derivatives," although the last two headings were used for other items. A curious inconsistency in *Biological Abstracts*' cross references is its placing of an article which in the title refers to 2-methyl-1,4-naphthoquinone (*Biol. Abs.*, **23**, 15162) under "Vitamin K_3" rather than with the other one under "Naphthoquinone, 1,4-, 2-methyl-," to which there is a "see also" reference from the former heading. For an article which discussed the use of Benadryl in four cases of nausea and vomiting due to streptomycin (*Biol. Abs.*, **23**, 15055) in which Antistin was subsequently substituted with effectiveness in one of the cases, no mention was made of the use of Antistin either in the abstract or in the indexing. This article was not indexed under "Histamine, antagonists," but merely under "Diphenhydramine" (Benadryl) and "Streptomycin." One cannot complain of *Biological Abstracts*' disease indexing. Of the three headings in the 1950 index under "Hetrazan, in treatment of filariasis," all are under "Filariasis." Though only one has the subheading "therapy with Hetrazan," the other two are subheaded "therapy with piperazine compounds."

Chemisches Zentralblatt has a great many headings under trade names of drugs as well as under their common names. There is no heading in the 1951 subject index under "Filariasis" or "Filariosis," although the entry under "Hetrazan" indicates that there are two papers on its use in the treatment of filariasis. Trade and common names are listed under such headings as "Arzneimittel" and "Droge," as well as directly. In its subject index, *Chemisches Zentralblatt* does not often index under the chemical name, relying instead on the formula index to bring out specific chemicals.

For *Excerpta Medica* only four section indexes for 1953 and one for 1951 were studied. Those for 1953 approach "catch-word" indexing more closely than any of the other indexes examined. For an article which was indexed under "PAS, intolerance" in Section XV (Tuberculosis and Pulmonary Diseases), an extra heading "Intolerance to PAS" seems useless to anyone familiar with systematic indexes, as it is the only "Intolerance" entry used. One would find an article on the isopropyl hydrazide of isonicotinic acid only through the use of imagination and possibly a bit of free association, because the heading under which it is placed, "Isopropyl acid hydrazide," happens to follow alphabetically a cross reference from "Isonicotinic acid hydrazide" to "INH."

Inconsistency between sections is to be anticipated. In Section XV (Tuberculosis and Pulmonary Diseases), such headings as "Bronchial," "Pulmonary," etc., stand alone in the main alphabet without further explanation, a practice which would not be possible in other sections. The only general observations on cross references possible are that there is no consistency between sections and there are not enough.

It was painfully easy to find omissions of drug entries. A paper on effects of streptomycin, PAS, and TB_6 on blood coagulation (*Excerpta Medica*, **XV**, **6**, 2144) appears under both "Blood, coagulation" and "Coagulation" but not under any of the individual drugs. In Section VI (Internal Medicine) there is a heading under "Diseases, Besnier-Boeck, treatment with streptomycin-PAS." Under "Streptomycin" a corresponding citation is found, but not under "PAS." In Section XI (Oto-, Rhino-, Laryngology) there is a heading "Otitis media, dipenicillin treatment," but the article is not under "Penicillin" and no "Dipenicillin" entry was found.

Different articles on the same drug were found under different headings in Section XII (Ophthalmology) where both "Compound F" and "Hydrocortisone" are used with no cross references to show they are the same. Entries and their sub-

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divisions are frequently so broad that all must be looked up to ensure a complete search. Cross references under "Streptomycin, and INH," "Streptomycin, and PAS," and "INH, streptomycin and PAS" in Section XV all say "see also under Combined therapy." Under "Combined" there are five references with no mention of the specific drugs. A heading "Chemotherapy" has only the subheadings "in tb" and "in tb, general" for the 15 citations given.

In contrast, the late-appearing index for Section II of *Excerpta Medica* (Physiology, Biochemistry, and Pharmacology) is excellent. There are individual entries for drugs under their chemical names, using *Chemical Abstracts* practices, or with cross references from the chemical name to the trade or generic name used. Papers are indexed both by drugs used and by their physiologic or pharmacologic effects.

Discussion

Though many of these observations are random and some counts undoubtedly atypical, the study has made it possible to change impressions from subjective to objective ones.

Current List of Medical Literature is the most prompt of all, both because of its 3- to 4-month lag in coverage of important English-language journals in the field and because of its monthly subject indexes. Considering their promptness, these indexes are very well done. But their lumping together of groups of drugs and occasional inconsistencies in nomenclature make them difficult and time-consuming to use. They do not index all articles under the drugs used. Only about two fifths of the current journals received in pharmaceutical libraries are covered, and certain kinds of articles such as abstracts of meeting papers are omitted.

Quarterly Cumulative Index Medicus has a minimum time lag at present of 19 to 20 months between publication of an article and receipt of its index. Though its coverage of the medical journals on its periodical list is thorough, it includes only a little more than a third of the journals received by pharmaceutical libraries, and it omits most items other than signed scientific articles. Defects in its index are: Cross reference is made from a drug to general headings, where perhaps only one pertinent entry will be found in several columns; drugs are collected into even broader classes than those in the *Current List of Medical Literature;* and individual drugs used in a study are sometimes not indexed at all.

Chemical Abstracts is fairly prompt with respect to abstract publication, though not consistently so. Its average article-abstract lag for important English-language journals is about 5 months. Its record of inclusion on its periodical list of two thirds of the current journals from the "Union List of Periodicals in Pharmaceutical Libraries" means very little because relatively few therapeutic items are abstracted, even though they appear in listed journals. Its subject index is most complete and easiest and quickest to use of all those studied, but its relatively late appearance is regrettable.

Chemisches Zentralblatt is an excellent abstracting publication, but use is hampered by the very late appearance of its index. Its point of view is least clinical of the publications studied. The time lag between publication of an article and of its abstract varies greatly, but may average about a year. Its index seems accurate and systematic, the formula index supplying information on specific drugs. But it does not index disease therapy.

Excerpta Medica is most difficult to use as a single reference work because of its issuance in sections. The article-abstract interval is perhaps 9 or 10 months, but the subject indexes for half of the sections appear promptly. The prompt-appearing indexes are least reliable of all those studied, while the one for Section II, which appears late, is excellent. The service covers only a little more than a third of the periodicals received in pharmaceutical libraries and does not cover all medical science items in them.

Biological Abstracts has an average time lag of 0.66 to 0.9 year between article and abstract publication, and its index appears later than that of any other service studied. Specific drugs are frequently lumped into groups in the index and are sometimes not indexed at all. It includes on its periodical list about two fifths of the periodicals currently received in pharmaceutical libraries, but the actual inclusion of articles from these journals is very inconsistent.

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British Abstracts of Medical Sciences is so new that it has issued no index or list of periodicals covered. The only study made was for time lag between journal and abstract publication. It is unfortunate that it has started with an article-abstract interval of considerably more than 7 months.

Other studies to fill out the picture might examine the pharmaceutical emphasis of individual abstracts in the publications here investigated as well as services in special subject fields.

Conclusions

The authors are impressed by the frequent excellence of the services studied for the purposes for which they are intended. However, no single service is adequate for reference work in a pharmaceutical library, and even a combination of all of them is not sufficient.

Inadequacies. Even the best of them is far from prompt enough in its indexing to provide answers to many of the questions which are received daily. A maximum of 2 weeks is necessary between appearance of article and of index in order to avoid supplementary work in individual libraries.

In order to have a reasonable coverage of all journals of interest all services should be checked, and even then there will be omissions.

No single service lists most of the important pharmaceutical papers. *Chemical Abstracts*, *Chemisches Zentralblatt*, *Biological Abstracts*, and to a lesser extent *Excerpta Medica* omit some important pharmaceutical papers occurring in journals they are listed as abstracting.

Many peripheral items of interest are not listed by any of the services studied. The most important class is the abstracts of meeting papers, where important new work is apt to appear.

The grouping together of drugs by class makes use of the medical and biological indexes time-consuming, but the chemical indexes, which list drugs individually, cover comparatively few therapeutic articles.

The combined use of all services does not ensure finding all important published information on a drug. Though some of the omissions cited are minor, the fact that so many were found readily indicates the probability of many more.

What can be done about these inadequacies? For some time possible answers have been studied *(1, 9, 10)*. It is hoped that this study will stimulate interest in establishing a pharmaceutical service or making an existing service more adequate to the pharmaceutical field. In the meantime, a recognition of their advantages and limitations should increase efficient use of the existing services.

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Aids to Progress in Research

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A questionnaire survey by a particular company indicates the need for up-to-date methods of abstracting and distributing patents and patent literature. A valuable procedure is presented for setting up a patent abstract file to aid the research chemist and to keep abreast with current United States and foreign patents.

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The future of patent research presents itself as an important factor in the growth of every technical corporation, and as such, it has been the topic of several excellent literature articles in recent years.

Bakalar *(1)* states: "The corporate or house patent department is a service unit.... The patent department is obligated to perform the following tasks: to stimulate research and accelerate development programs as by predigested patent surveys and by the segregation of usable know-how in patents; to post management, in timely fashion, on competitive efforts and trends based on subject information."

Frankl *(3)* indicates that "it should, therefore, be one of the functions of a company's patent department to develop for the research department a quick but thorough orientation in the rapidly changing patent situation by acting, so to speak, as a commentator on the daily news as offered by the Patent Office."

Krase *(4)* related in a recent article that "regular reading of new patents is another important factor in stimulating the flow of new ideas in research groups. . . . Appropriate classes of these patents should be ordered and made available by the organization, and research chemists should be encouraged to read these with the same diligence that is devoted to current chemical periodicals. By faithful attention to this branch of chemical literature a practical knowledge of developments by competing companies can be acquired."

Timeliness

Clearly, the stress is on timely commentaries. Previous experience of predecessors and supervisors of this author has shown that within a research, development, and production group, while located within several city blocks of each other and all served by the same house distribution system, patents reached the last name on their circulation lists sometimes six months to a year after leaving the corporate patent office. The percentage of loss was proportionally increased by the length of time required to complete the circulation, and the need of recalling the patent for special demands was fraught with delay and troubles, often necessitating the purchase of additional copies or costly photostats. New personnel added to circulation lists increased the circulation time required, and it was difficult to bring new personnel up to date in any field.

In addition to problems thus faced by the corporate patent department, the problems arising for the chemist were further multiplying. The importance of following patent material for its news value was lost, for, faced with the need of keeping up with their own and other interests, many research personnel subscribed to patents cataloged by the former system within this department under 20 or more categories. A system can in no way compensate for the valuable time spent by the chemist and management in reading or even attempting to read the volume of material routed to them.

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Reading Tests or Survey

Results of adult reading tests given personnel, in connection with reading improvement courses being conducted under company sponsorship, showed that the over-all reading speed average (before training) was less than 300 words per minute, more like 275 words per minute. A random check of ten patents recently abstracted by this service showed the patent to average 2236 words while the corresponding abstract contained 108 words. Allowing approximately 10 to 15 minutes maximum time for preparing the original abstract, and 5 to 10 minutes for the copy work by clerical help, the chemist's expensive time is left open for creative research and the less valuable time of clerical help carried the burden which was multiplied 100 times as each single abstract served its purpose. Thus, the "reluctance which many chemists show to study patents" as described by Frankl *(3)* in his article grew, and the need for a new system was given emphasis.

Company Dissemination of Patent Material

To put a new system into effect, letters were sent to several pharmaceutical and allied firms inquiring about their experiences in dissemination of patent material. The response was most gratifying.

Almost every concern seemed to be interested in this problem. Of the dozen companies whose responses have been completely studied, and who agreed to allow this author to use their opinions and cite their procedures at will in this presentation, only two subscribe to extramural patent abstracting services, and in each case the material thus obtained is carried to some extent by their own library information bulletins.

The publication of an information or abstract bulletin, however, seemed to be unanimous. In several cases, particularly where the technical library staff handles both the literature and patent material, the regular bulletin may contain data covering new accessions by the library in both bound and periodical form, as well as current literature references and new patents, and may not differentiate between the listings of literature and patent references under broad subjects of interest to personnel concerned. The publication dates of the majority seemed to be weekly, with special supplementary lists issued monthly in some cases. In one case where no bulletin is published, weekly memos concerning eight to ten patents keep the president and key technical personnel abreast of happenings in fields important to the growth of their interests. In one case, the abstracts for the United States patents are circulated as copied from the *Gazette* weekly as the patents are ordered, and telephone requests are taken to be filled when the desired patent is received.

Because the literature emphasized the value of patents in relation to reflections of competitive efforts, it was surprising to find that two firms either definitely stated that they did not cover patents other than United States, or failed to mention or show any reference to foreign issuance. Contrary to this, this organization subscribes to ten foreign periodicals or services covering foreign listings, with special attention to specifications even though not yet available in Australia and South Africa. As such items appear they have a special listing, by country, at the end of the weekly Patent Abstracts under the heading Foreign Applications Pending.

As hoped, several suggestions were received for the improvement of this company's publication as a result of the correspondence. Several sources suggested the use of perforated paper, card stock, or individual slips which could be sent for separation by the chemist himself, or separated by library or patent department clerical help and only items of specific interest distributed to interested personnel. This suggestion as yet has not been followed by this group, but another one, that of clearer divisions of the subject groupings and the setting forth of the patent numbers, has improved the appearance and usefulness of this publication.

Questionnaire

In the company's original letter a question was included with regard to the value of such a project from a cost standpoint and in personnel satisfaction. In almost every case, special comment was made by those directing this type of work as to the value, not so much resulting from an extensive time-cost analysis, but from the enthusiastic response, the development of interest with education on patent use, and

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the cheap source of information, especially during the interim between the publication of the corporate Patent Abstracts and such standard sources as *Chemical Abstracts*. Coupled with these comments came such remarks as "files used all of the time" and "feel that publication is regularly studied," which further encouraged the setting up of the present system. Encouraged by the fact that only one company replying felt that such a program was inadvisable for it, and that even this company found some type of a system specifically suited to each and every branch or division widely scattered throughout the United States, the following program was established.

With reference to some of the responses received, Mathys *(5)* can be quoted in support of this system: "It is seldom necessary or even desirable for anyone looking for technical information to read the claims at all," while, "the title; this is not very instructive and although sometimes used in libraries for classification purposes, it is wholly unsuitable for that purpose."

Suggested Program

Each periodical is entered in receipt by the order clerk and is quickly checked for possible items of interest which are called to the attention of the chief patent attorney or one of his legal assistants. Items on this list are marked as order, PA, A, or C. The periodical is then returned to the order clerk, who proceeds with the order from her source. Items marked PA are for Patent Abstracts, without order. *Pink* number cards are made for these for the number file, and the *white* subject cards are used to prepare the next Patent Abstracts issue using the title with inventor, assignee, etc. If others feel the necessity of seeing such items, they may be ordered at their request, and standard white number (order) cards are prepared.

Items bearing an A designation are given white subject cards only, and as such go directly into the 3 × 5 *subject card file* to be used in the future in event of a search. These are usually *foreign items* of which the United States, British, and Canadian patents are already on file, or subjects which at present are not being followed in a definite program within the laboratories, but are under extensive work by competing manufacturers or may come into use at a later date in the opinion of attorneys.

The C cards are reserved only for *foreign pending* applications not yet available, and are kept in a separate file on the desk of the order clerk, who watches for these numbers in subsequent "Open to Public Inspection" listings. Such card arrangement, once prepared, is infinite. Often it is of advantage to cull out all cards on a subject which is of interest only to a few. By the use of a *bibliographic* type of arrangement, three to six carbon copies may be made by an unskilled typist and a selected subject list is given to specific personnel for their laboratory files. This particularly pertains to material such as covered by the A cards. This system provides an opportunity to reach all pertinent subject matter and at the same time to publish effectively all items of general interest, with essentially the same techniques, enabling the staff to publish specific lists for definite purposes with a minimum amount of effort.

Ordered Items

As the *ordered* items are received, they are first sent to the abstractor, where they receive the subject headings and the abstract card is typed. Based on previous experience with subject headings, and faced with the possibility of employing personnel without technical background for such a position, the company's pharmaceutical interest is emphasized and the "primary" subject headings are in the *utility* category whenever possible. At this point the idea followed is that expressed by Bennett *(2)*: "It is not unusual for any specification to be classified under five or more headings."

The *primary* headings are typed in red, five spaces from the upper left-hand corner of the first line of the 3 × 5 subject card, and also on the upper right-hand corner of the patent itself. The first listing is the subject under which the 3 × 5 subject card with the *full abstract* is found, and also the subject of the vertical file wherein the patent remains whenever not in use. Also, on the first line at the upper right-hand corner of the subject card is the country of issuance and the patent number.

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Classification

The second line, at the outer left-hand margin of the card, bears the *secondary* subject heading. This point has been of greatest value in this work for present and future search efforts. This secondary subject is in almost all instances chemical, adapted from the company's very simplified Beilstein system. Within this system this organization does not follow the proper Beilstein idea of last possible place, but tries to establish the most important place. Also, no differentiation is made between aliphatic and aromatic as in the ketones, since from the pharmaceutical point of view they are received in the same manner. Large groups—such as the amines—are broken down into primary, secondary, tertiary, and quaternary, but the halides are grouped as such.

On the third line of the card, five spaces in, the *title* of the patent appears in capital letters. This title is followed directly by the *abstract* in parentheses. To obtain this abstract, attention is called to the section of the patent known as the *specifications*. Frequently, key sentences are copied verbatim. Often the chemical formula is depicted and the *R* substituents listed. Where possible, synthesis methods are suggested and any relationship between trade-marked compounds or commonly used compounds is pointed out. The existence of charts or tables is mentioned and in the case of patents dealing with apparatus the number of pages containing drawings is cited.

At the end of each abstract, two lines down and even with the left-hand margin, appear the country of *issuance* and the *patent number*. Directly below this is (are) the inventor(s). In the center of the card, on the same line as the patent number, appears the *assignee*, and below that the *date of granting*.

Cross references are brought out to the left-hand margin under the inventor(s). Cross reference cards follow the same form, omitting the full abstract and putting in its place in parentheses (See also, primary heading).

Completed cards are attached to the patent and are sent to the chief patent attorney, who regards this as an opportunity to see all incoming patents and to limit the scope of abstracts selected for publication. Those cards set aside at this point are filed directly in the subject card file, and do not appear in the Patent Abstracts publication. This procedure allows the chief patent attorney to tailor the publication to suit the needs of the research staff and their most current interests, without interference with the scope of the card index and serves as a means for preventing the publication from becoming needlessly voluminous. The cards are then returned to the general clerical worker who makes the important cross-reference cards and puts all subject cards into the box marked "for PA."

Patent Bulletins

Weekly Patent Abstracts bulletins are prepared from the cards within this box. The cards are arranged alphabetically in large subject groupings: antibiotics, enzymes, etc. From this arrangement, the stencil for a current circulation of 175 to 180 subscribers is prepared.

When the stencil has been proofread, the cards are placed in the box to be filed. The subject files into which these cards are put form the backbone of this system.

Other authors often have cited the value of such files, and as Bennett *(2)* states, "the hardest and possibly most common type of investigation that a searcher makes is a subject-matter search." Schaler *(6)* indicates that such "search procedure in a specialized industry can be simplified and shortened immeasurably by use of a highly flexible subject index system . . . and accumulated cards . . . form a series of continuous searches on the class subjects," while "routine abstracting and indexing keeps these collections constantly up to date."

Filing Rules

Again accepting the fact that for nontechnical personnel a strictly chemical filing system would be hopeless, the cards are filed according to the following rules:

1. Alphabetically according to *primary subject.* 2. Alphabetically within the primary heading by secondary heading, leaving cards with no secondary heading to come first. 3. Alphabetically by country of issuance under these headings, with the exception that the United States patents come first. 4. Numerically under the country, with application numbers preceding patent numbers, and the highest numbers being at the end.

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Operation of System

The value of the system, at present about one year old, is becoming clearer every day. A recent request for a Belgian patent was checked subjectwise and the corresponding British equivalent was found already to be in the company's possession, thus satisfying the reader as to a point of interest. Another day, a reader wished to know if there were any patents of a particular corporation available on compounds related to a certain well-known pharmaceutical compound. A knowledge of the chemical formula of the pharmaceutical compound was all that was necessary to locate a South African patent available in the files under hypnotics, cross-referenced under anesthetics and anticonvulsants, all bearing the secondary subject "alcohols" and entitled "unsaturated tertiary carbinols and their esters and lower alkyl ethers, etc." by the specific corporation, together with the date of issue of the patent.

Owing to the demand, two lists are now issued by this method. Irregularly, the weekly abstract bears the bold face heading Apparatus and Special Techniques Issue. As befitting a pharmaceutical house in general, and Abbott Laboratories in particular, this list contains nothing but items pertaining to transfusion apparatus, containers for medicinals, the preparation of capsules, ampoules, etc. This list does not circulate as widely, having only 65 to 70 subscribers on its distribution list, but it has also received enthusiastic response and effectively separates the two largest fields of interest—the preparation of medicinals and their marketable aspects.

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Statistics

The regular list has a circulation of 175 to 180, and the apparatus list has a following of 65 to 70. Of the 24 issues published during 1953, the average number of pages was 13.5; the average number of patents cited was 45.5; from 6 to 25 different people responded to a single list indicating the desire and need to see from 9 to 71 specific items. Many subscribers say that they often find the answer to their immediate needs within the abstract itself, and that they save specific abstracts in personal files for future requests or reference.

Future Prospects

Future evaluation of this problem of the dissemination of patent information will doubtless lead to new approaches as the establishment of this program and the correspondence leading thereto has already proved for this organization. Specific problems arise in each and every field of endeavor. In the fast developing field of scientific literature, to say nothing of the increasing volume of patents issued, a panacea is unlikely to be developed very quickly and certainly not without the efforts of many and the failures of a few.

These efforts have improved the immediate position and have alleviated to some extent a pressing need, felt by valuable scientific personnel, to carry the burden of increased demands upon their time. Present and future uses of such a versatile system, capable in many ways of being carried on by semiskilled personnel, while serving the needs of a variety of technical personnel, can scarcely be fathomed, but efforts made toward improvement will doubtless prove their worth.

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Pharmaceutical Patents in Foreign Countries

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Practices in foreign patent offices with respect to pharmaceutical inventions are compared with those of the United States Patent Office. This paper reviews the various complex factors affecting pharmaceutical patents with details for drafting of foreign specifications and claims to secure full protection for pharmaceutical inventions.

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There is not likely to be disagreement with the general proposition that the financial health of a pharmaceutical manufacturer in these competitive days depends largely on efficient research, which results in the creation of new inventions, and their protection by United States patents. Successful research is costly and often can be adequately sustained only by an increase in production and sales, so that pharmaceutical manufacturers are turning more and more to foreign markets as a supplement to their basic United States markets, and in some instances are making products specifically intended for foreign requirements. The various needs in foreign countries for United States products and know-how are so great that there is little doubt this trend will continue and grow. In spite of the uneasy political situation, dollars are usually made available for pharmaceutical purchases. Foreign patents to protect activities abroad are therefore becoming of increasing importance to the United States pharmaceutical manufacturer.

Pharmaceutical Research and Foreign Patents

Three principal reasons for obtaining foreign patents are as assurance of the *prima facie* right to maintain imports, as a source of revenue from licensees, and as protection for manufacture by subsidiaries or affiliated companies.

Problems, and often difficult ones, also begin when foreign patent applications are contemplated. Any invention which is not patented in a foreign country can be used freely by foreign competitors. Also, all United States inventions cannot be protected in all foreign countries. The practical solution must lie between these extremes. The United States pharmaceutical manufacturer who is active abroad should therefore have a definite foreign patent policy for consideration and evaluation of inventions, so that those of importance can be protected abroad in an orderly manner—if, where, and when desired.

Publication and Use, and Timing of Foreign Filing

Executives in charge of a company's foreign patent policy, even though not responsible for detailed handling, should have some acquaintance with essential differences between United States and foreign patent laws and regulations, and also the international arrangements which a United States applicant can use. Inventors and clinical investigators in the pharmaceutical field are usually anxious to publish their results as soon as possible, and sales managers are eager to ship new products to their distributors. But such publication and use may automatically destroy the possibility of securing valid foreign patents. There are many sad examples of rushing into print in haste, and repenting at leisure.

First and foremost, no publication or commercial use should take place *before* the United States patent application is filed; although harmless under the United States patent law for one year, this in general is not so in any other important country except Canada. Secondly, after the United States application has been filed, decisions concerning foreign filing, when to release publication, and when to

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permit use must be made at appropriate times if full benefits are to be secured in the foreign field.

The International Convention, which permits the benefit of the United States filing date to be claimed in a foreign country within one year, irrespective of any intervening publication or use, is of course a vast help—and most important countries are members of the International Convention. (This is one of the few international treaties which has survived two wars and is universally applauded as a sensible arrangement.) There is also the Buenos Aires Convention, having similar priority provisions, to which the United States and a number of Latin American countries belong, and which is of use in those not belonging to the International Convention. In addition, the Interdominion Arrangement among the British group enables a Canadian filing date to be claimed within one year in India and Pakistan, which are not yet members of the International Convention. However, a few important countries, mostly in Latin America—such as Argentina and Chile—are entirely outside these mutually protective arrangements. It is true that some of these permit patents of confirmation, whereby a patent can be obtained corresponding to an issued patent in another country, irrespective of any publication, provided there has been no use within the country. However, in view of the widespread international distribution of pharmaceuticals, it may not be safe to wait for a patent of confirmation.

The United States pharmaceutical manufacturer is almost always in a serious dilemma when considering foreign filing and balancing costs against potential advantages. It may take several years after the filing date of a United States patent application to test a new product. Should foreign filing be delayed until it is certain the product is valuable? Even if there is no publication or use, such delay may be dangerous, since, in view of competitive research, others may in the meantime have obtained dominating foreign patents. It is certainly safer to file within the priority year in convention countries, and as promptly as possible in the nonconvention countries; once foreign filing has actually been effected, any subsequent publication and use can have no harmful effect.

A given situation must be judged on its merits; the important thing is to be aware of the essential foreign provisions, so that any failure to obtain foreign protection will be deliberate and not an unwelcome surprise.

Where to File Foreign Patent Applications

If a decision has been made to file abroad corresponding to a United States patent application, and no bars exist through prior publication or use, the next question is—where?

There are no easy answers. For an invention relating to a printing press, for example, or the beneficiation of a special ore, there may be only one or two foreign countries which would be sources of either profit or infringement. However, a different situation exists with respect to pharmaceutical inventions, since manufacture may take place, not only in the major countries, but also in small or semi-industrialized countries where populations are increasing and the governments are interested in public health. If the invention relates to an improvement in a known process, or a new product having only specialized uses, no foreign filing at all may be warranted, or only in a few selected countries where manufacturing licensees may be operating. But if no foreign patents are obtained on an important new product—such as a new antibiotic—it could be copied by competitors in numerous countries for both their own domestic market and export to other consumer countries. Apart from the loss of revenue to the United States patentee, uncontrolled foreign competition can flood world markets with material of poor quality.

For any new pharmaceutical product with important potentialities, the principal sources of foreign competition should be plugged with patents. As a practical matter, this means England and most of the European countries, Canada and certain Latin American countries, Japan, Australia, South Africa, and India—ignoring the countries behind the Iron Curtain.

It is hardly a headline item that European manufacturers are developing worldwide markets, and are building up foreign patent positions. In particular, the German pharmaceutical industry is becoming very active abroad, especially in the

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Near East and Far East, and is also beginning to regain some of its prewar influence in Latin America.

The United States manufacturer, thus faced with numerous problems of probable and possible competition abroad, can only apply the rule of reason when selecting foreign countries in which to file patent applications for a pharmaceutical invention, plus a certain amount of gambling instinct. Assuming that convention priority is being claimed where possible, so that the decision is made less than a year from the United States filing date, it is usually far too soon to evaluate the true importance of the invention. If the product is good, infringers will look for loopholes; if it is unsuccessful, the whole foreign patent program may be useless.

Three other factors must also be considered in selecting individual countries and determining the use and value of foreign patents: the type of protection possible—i.e., whether product and/or process claims are obtainable, the working provisions in foreign patent laws, and whether patents will prevent importation of products.

Product and Process Claims

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The United States patent system permits independent product claims for new pharmaceutical products, not limited to the process of manufacture. Apart from a few notable exceptions, this is not the case at the present time in numerous foreign countries, where the nature of the patent protection granted to pharmaceutical inventions is the subject of much debate and reappraisal. Extremely conflicting viewpoints have not yet been resolved as regards the basic problem—are the interests of the public best served by a broad monopoly in the product, or by a limited monopoly restricted to the product as made by the process actually disclosed?

There is a considerable amount of history involved in this situation, and it is probably simpler to start in the middle and review European ideas, particularly in the highly industrialized countries.

The limitation of protection for chemical products in general, as well as pharmaceutical products in particular, to process claims, is essentially a continental European conception, and is tied up with social thinking in the nineteenth century during the industrial revolution. It became a matter of practically unassailable dogma that if the public is to receive the benefit of new chemical or pharmaceutical products at a reasonable price and in amounts sufficient to meet the demand, this could be accomplished only by restricting the inventor to his process, so that others would be encouraged to invent new and improved processes which make the product cheaper and available in greater quantity. Probably there was also the fear that with so many closely adjacent countries, product claims would enable the manufacturer in one country to obtain effective control of the entire European market. Switzerland was so fearful of foreign domination that it adopted the excessively strict requirement that one patent could cover the process of making only one specific chemical or pharmaceutical product—which has actually resulted in the proliferation of Swiss patents and much benefit to Swiss patent lawyers. However, Switzerland is an exception, and other European countries permit broad process claims when the product is new. These European ideas regarding the desirability of process limitation for pharmaceutical inventions were transplanted many years ago to numerous other regions and particularly to certain Latin American and Far Eastern countries.

The British viewpoint of the nineteenth century was different and product claims were then permitted. However, the process limitation was introduced in 1919, largely as a result of numerous broad product claims for dyestuffs obtained by German inventors before World War I and the fear of domination of the British industry by German interests. Some of the major British colonies followed suit; some did not. After 30 years, there has now been another about face. In the new 1949 British Patent Act, independent product claims are again permitted.

This somewhat unexpected but logical change in British practice has had a profound effect in European patent circles. In many countries now permitting only process claims, the desirability of independent product claims in patents for new pharmaceutical products is being most carefully considered on the ground that in view of present conditions and the enormous expansion of the chemical and pharmaceutical industries, limitation to process protection may be outmoded and actually harmful. The number of new compounds that can be created is so great, the spur of com-

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petition is so strong, and the cost of research is so large that no manufacturer rests on his oars after placing a new product on the market, and will himself continue to work on improved methods of production. From the viewpoint of the public interest and the commercial utilization of a new product, all the novelty and advantages actually reside in the product itself, and it is immaterial whether the product is produced by an entirely new reaction or by a conventional reaction. If the reaction process itself is new, this in turn promotes research to utilize it in the production of other new products. It can be argued vigorously that in countries in which patent office practice holds that utilization of a known process to produce a new product is obvious, research is actually stifled. The public benefits from the product and not from the process.

It is of interest and significance that in June 1954 at the Brussels Congress of the International Association for the Protection of Industrial Property (the unofficial organization for study and consideration of revisions to the International Convention) a resolution was adopted recommending the introduction of a new article binding each country to admit the patentability of chemical products, subject to certain reservations.

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This liberal tendency in Europe is simultaneously being matched in certain other countries by an extremely antagonistic attitude toward pharmaceutical patents in general. In Italy, no pharmaceutical patents whatever have been granted for some ten years. The Italian Patent Office interprets the patent law as excluding even process protection. As a result numerous appeals have been filed. The Appeal Commission has compromised to the extent that process protection is admitted if it is proved that other processes exist for making the product. However, the Italian Supreme Court has held that the whole prohibition is unconstitutional. Apparently, a solution can be found only if the Italian patent law is amended. In France, the grant of all pharmaceutical patents has been held up for many years. Two opposing factions have been debating whether any protection should be granted for pharmaceutical inventions. In the meantime the French Patent Office has required a declaration from all applicants in pharmaceutical cases that protection resides entirely in the process and not in the product. Recently (in 1955) a special examining board was created, but is apparently inactive and a number of pharmaceutical patents have at last been granted.

Why should Italy and France adopt such a viewpoint which is so contrary to that of other technically developed countries? Principally this is a result of the war. In Italy, the pharmaceutical industry was so badly damaged and disorganized that it was slipping backward in the competitive postwar race. There is no doubt that the Italian pharmaceutical industry itself exerted political pressure and was directly responsible for the patent situation; it was willing to forego any patent protection of its own, provided it could copy United States and other pharmaceutical inventions for domestic and export markets. At the present time, Italian research is growing, and the attitude toward patents has become somewhat less antagonistic; however, the situation (in 1955) as regards grant of pharmaceutical patents is still entirely obscure. This is a specialized instance of the impact of economics on patent law, involving the belief that the grant of pharmaceutical patents to foreigners would actually destroy or retard the domestic industry. In France, the situation was not entirely comparable or the attitude so drastic, but it is true that a considerable section of the French pharmaceutical industry considered its interests might best be served without any patent protection but with freedom to pirate foreign inventions. It is encouraging that a less radical viewpoint now appears to be gaining the day.

If countries like Italy and France suffer from such fears, it is understandable that other less developed countries, or those in a precarious economic condition, have also placed difficulties in the way of foreigners wishing to obtain pharmaceutical patents. Within the past few years, several Latin American countries, starting with Argentina and now including Brazil and Mexico—which in any event do not permit independent pharmaceutical product claims—have begun imposing drastic limitations on broad process claims. The Mexican Patent Office even insists they must be limited to the preparation of specific compounds using specific reaction conditions. A typical statement in many Mexican Official Actions now reads: "General processes of synthesis of chemical products are not patentable in accordance with

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Article 6 of the Patent Law. However, patents may be applied for covering the preparation of the specific chemical products in the original application which are capable of industrial exploitation."

It is difficult to predict how all this will develop in the next few years; the only hope is that the line of division between the opposed viewpoints will not grow deeper.

Working and Compulsory Licensing

The patent laws of practically all the major foreign countries state that an invention should be worked usually within three years from the date of grant. By "working" it is meant carrying out the invention defined in the claims of the patent, within the foreign country, to an extent sufficient to meet the full requirements of the public at a reasonable price—that is, for a pharmaceutical product, it should be manufactured within the country and not imported. The foreign working provisions constitute a further great distinction between United States and foreign practice. The theory is that an unused monopoly is not in the public interest, and in effect hangs like a club over industry for the life of the patent and hinders further development. This, of course, is a debatable proposition. However, as a practical matter, the penalty for nonworking is not too serious. In a few relatively minor countries, a patent may actually be subjected to attack by third parties or invalidated by the patent office or courts for nonworking, but in the important convention countries, the preferred remedy for nonworking is "compulsory licensing." This term has been widely misunderstood and to a considerable extent is not as compulsory as it sounds. Very few compulsory licenses are actually granted in convention countries for patents in most fields, though the situation is somewhat stricter for pharmaceutical inventions. To obtain a compulsory license, a third party must file a petition to establish that he is able to supply the public demand at a reasonable price by manufacture within the country. The patent office, after full consideration of all the facts, including objections by the patentee, has discretion to determine whether or not a compulsory license should be granted and if so, what royalties should be awarded to the patentee. In actual practice, a potential licensee usually approaches the patentee for a voluntary license, and it is only in the event that an amicable settlement cannot be reached, that compulsory license proceedings are begun. The normal period for working for most countries begins three years from the date of grant of the patent. However, in England, and in a number of British dominions and possessions, where a pharmaceutical invention is involved, a third party can petition for a license immediately the patent is granted.

The rule of reason also applies to compulsory licensing. If a pharmaceutical product is not successful, no one is likely to ask for a license. However, if the product is of major importance, the United States owner of foreign patents must be prepared to face the fact that if he does not manufacture abroad, he may have to share the market with foreign manufacturers, subject to royalty payments.

Importation of Products

A very important question for United States pharmaceutical manufacturers, both offensively and defensively, is—do foreign pharmaceutical patents prohibit importation of the product? It can be stated categorically that in Europe and in practically all important countries outside Latin America, they do, and in general process claims are regarded as inherently including the immediate product thereof. The burden of proof as to whether the product is actually made by the claimed process is in general either on the infringer or the patentee, depending on whether the product is new or old. However, in a large number of countries in Latin America, it is considered that process claims do *not* cover the product, and since product claims are not permitted, it follows that process claims cannot be used to stop importation of the product. In the absence of much patent litigation in these countries, to some extent this is a matter of opinion, and consequently there is a strong tendency to settle important disputes by negotiation.

Patents for Mixtures

The protection of mixtures, as distinguished from products of a chemical reaction, is difficult, to say the least—that is, where known ingredients having pharma-

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ceutical properties are mixed with other known ingredients which in themselves may be pharmaceuticals or carriers or extenders. Should the public be prevented from buying and mixing ordinary and well-known compounds? If not, what can be regarded as patentable in a mixture? What is not patentable is probably best expressed in the British patent law as follows: "If it appears to the comptroller in the case of any application for a patent that it claims as an invention a substance capable of being used as food or medicine which is a mixture of known ingredients possessing only the aggregate of the known properties of the ingredients, or that it claims as an invention the process producing such a substance by mere mixture, he may refuse the application." In general, all the important countries having a strict examination use this criterion, some more stringently than others. An unexpected effect, beyond the aggregate of the known properties, requires synergism, involving some form of interaction of the ingredients in the mixture as distinguished from ordinary chemical reaction. The synergistic effects may be of widely different types —such as unexpected preservative or antiseptic properties, reduction of toxic effects, etc. There is probably a general tightening up in most patent offices in regard to mixtures; because some synergism between active compounds is more or less normal, examiners are looking for exceptional or unexpected synergism.

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Patents for Antibiotics

The protection of antibiotics constitutes a new and specialized branch of patent practice. In general, all basic antibiotic patents are similar in form, and inherently involve fermenting a specified organism in a nutrient medium. This sounds straightforward enough. Actually it is not, and patent practice is becoming involved in semantics. In the first place it is very rare that the identifying structural formula for a new antibiotic can be worked out by the time a patent application is ready to be filed; therefore the product is defined by name, which is nothing more than saying it is the product of fermenting the specified organism. The novelty then resides in discovering and using an organism, since fermentation techniques in themselves are old and conventional. Invention defined as discovery is treading on dangerous ground. It is probable that patents in countries permitting product claims are stronger than those having only process claims. The products can usually be defined precisely by their infrared spectra, although, in a few countries, examiners have tentatively proposed that antibiotics are actually natural products and may be found in nature in an appropriate environment. The situation is further complicated by the fact that the organisms themselves seem to be becoming elusive as generations multiply, and susceptible to very wide variations in morphological characteristics.

Until now basic antibiotic patents have been granted in very broad form in most countries throughout the world. However, some second thoughts seem to be in the air. In Brazil, the patent office has exploded a bomb in the form of a standard official action objecting to antibiotic process claims, which contains the following statements:

Since there is nothing new in the procedure for preparing the new antibiotic, and the applicant merely selected among the usual culture media the ones which are most suitable to the object in view, we are forced to the conclusion that the only characteristic feature of the process is the use of a certain strain of mold.

In the circumstances, the grant of a patent on this application would give the applicant a monopoly for the use of this species of mold in fermentation processes and consequently for the product (antibiotic) formed by the metabolism of a living creature belonging to the vegetable kingdom.

Although one can admit that the said antibiotic may in future be prepared by synthetic or other means, the fact remains that in this application what is claimed is the exclusive use—for this purpose—of a certain species of mold, which mold, although isolated and described by the applicant, is not the latter's invention since it pre-exists in nature.

We hold that this application should be rejected, since what is claimed is the exclusive use of a living thing belonging to the vegetable kingdom for the purpose stated, by means of a process which follows the known and usual general rules which are habitually observed in the production of antibiotics.

Many Brazilian pharmaceutical cases will be taken to appeal; however, it is impossible to predict how the appeals will be decided, and Brazil may have the dubious

distinction of being the first country to refuse antibiotic patents on alleged technological grounds—as distinguished from Italy and France where the present or past refusal is more on political or economic grounds.

Patents for the recovery of antibiotics from fermentation mashes and their purification by special techniques, which are of the greatest practical importance, are in a different category and encounter only the normal hazards of examination.

Selection of Countries

In the light of the above discussion, the following main factors should be considered when selecting foreign countries in which to obtain patents for pharmaceutical inventions:

The nature and potential importance of the invention, and whether in the absence of foreign patents copying would be a temptation for competitors.

Whether product or process claims could be obtained in a given country; whether such claims would be broad or limited; and whether they would provide protection against importation.

Whether the nature of the invention is such that it would only be used in a few countries, or would have a potential market throughout the world.

Whether the foreign patents would be used by existing or prospective licensees or affiliates, or would be intended primarily to protect export markets—bearing in mind the attitude toward pharmaceutical patents in the particular country and also the ultimate possibility that others might apply for compulsory licenses in the absence of domestic manufacture.

Form of Foreign Specification and Claims

Having decided on the filing of foreign patent applications, the next problem is to obtain the best possible patents in each country. The specifications of United States patent applications relating to pharmaceutical inventions are often not fully satisfactory in numerous foreign countries; this is something that United States patent attorneys should remember when dealing with inventions which may be filed abroad.

Product claims can be obtained under United States pratice, and in many instances the inventive subject matter, according to the viewpoint of the United States patent office, does not reside in using new reactants in a known process, but in the product itself. It is customary for a United States pharmaceutical specification to be casual and brief in its description and examples for preparing a new product by an old process, and sometimes it may even state that the method of preparation is obvious. However, in those foreign countries which do not permit product claims, only process claims can be obtained and these must be substantiated by adequate description and examples. Therefore, a plea is made that all United States pharmaceutical specifications which may also be filed abroad be prepared initially with full description of the process and representative examples; this may be surplusage according to United States practice, but it does no harm. Unnecessary description could, if necessary, be deleted or condensed during prosecution in the United States Patent Office.

The ideal specification for a pharmaceutical invention should include the following portions and then will be suitable for filing abroad, whether the particular country permits product claims or only process claims:

The introduction should refer to the generic name and nature of the product.

Any problems heretofore existing in the same general field should be mentioned, and the purpose of the invention in relation to elimination of such problems.

A clear definition of the product should be given, preferably by a structural formula; it should also be indicated whether or not the product is believed to be new.

A general statement should then be given of the method or alternative methods for making the product, indicating whether or not the process is believed to be new, is an improvement in a known process, or is a known process using new reactants.

The pharmaceutical and other identifying properties of the product should be set out, if it is new, with any appropriate chemical or clinical or other test data.

Specific examples of the process of preparation of the product should then be given, in sufficient number to illustrate the general formula.

On this basis, it should be possible to get the best out of the invention, whatever the individual practice in a given country. The statement as to novelty may have

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to be altered during prosecution, according to the prior art which is discovered. In all countries process claims should always be filed, even if the practice also allows product claims. If the product is later proved to be known, the process claims may still sustain validity.

It should also be kept in mind that a number of United States applications can often be advantageously combined into a single specification for many foreign countries. This may actually provide better and broader protection than a series of individual applications. The essential requirement for combining is that the subject matter should be susceptible to coverage by dominating claims. Also if the International Convention is to be claimed in countries permitting multiple priority, all the United States filing dates must be within a year of each other.

What Can Be Protected

The simplest type of pharmaceutical invention to claim is a single specific new compound. This can be fully defined verbally or by formula, and its preparation clearly exemplified. However, such cases are somewhat rare. More usually a new series of compounds is produced having a class formula. Whether or not a particular country permits product or only process claims, the problem is to define the range of the variables in the class formula. If there are substituents, such as alkyl or aryl groups, the number of carbon atoms or some other appropriate identification for the beginning and end of the range should be given, and specific examples should illustrate compounds throughout the range. In a well-known leading case in England, a general formula was proved to cover some millions of possible compounds, whereas only two compounds were specifically described. The British courts held the claims were "covetous" and the patent was declared invalid.

In some countries a new series of compounds is considered as a chemical invention with the pharmaceutical properties incidental. However, most countries require the pharmaceutical properties to be given in some detail, which is difficult at the early stage of development, in view of the time necessary for satisfactory clinical tests. Therefore, from the viewpoint of validity and obtaining strong pharmaceutical patents, it is probably better to limit the claims to new compounds for which the beneficial pharmaceutical properties have been positively demonstrated. If new compounds in a series are later found to have similar properties, these can usually be protected in patents of addition, for which no maintenance taxes are payable.

In England and most of the British Dominions, the patent office examination covers only novelty and form. However, in the strict European countries—such as Germany, Holland, and Sweden—it is necessary to establish not only novelty, but also "inventive height" and "advance in the art." The former can be considered as nonobviousness to an expert, and the latter as general utility. There is not much difficulty with a new product prepared by a new process. If the new product is merely the result of putting different reactants in a known process, there is trouble. This is called an "analogy process" and the patent will not be granted unless the new product has exceptional and unforeseen properties.

It would be very desirable for more pharmaceutical manufacturers to support the activities of the International Patent and Trademark Association, which is the new name for the United States group of the International Association for the Protection of Industrial Property (AIPPI). In 1956, the congress of AIPPI will be held for the first time in the United States, which will provide a unique opportunity to acquaint the foreign delegates with the United States viewpoints concerning patents and trade-marks in relationship to international trade, and in particular the desirability of a more uniform practice in convention countries concerning pharmaceutical patents and the protection afforded thereby. It is probable that observers will be sent to this congress from a number of Latin American countries which are not members of the International Convention; it is to be hoped that such observers will be welcomed and a vigorous effort made to persuade them of the numerous advantages of joining the International Convention.

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Pharmaceutical Trade-Marks in Foreign Countries

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Pharmaceutical trade-marks function as symbols and essential lines of scientific research and progress of medical science. Protection laws for trade-mark rights in foreign countries and United States against infringement, misappropriation, and piracy are discussed. International conventions contain valuable stipulations to harmonize conflicts of law to protect the rightful owner. Transformation of trade-marks into generic names are to be avoided.

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Trade-marks for pharmaceutical products are not different in nature from trade-marks for any other products—food products, electrical products, machinery, raw materials, and the like. They are adopted and used by manufacturers or dealers in pharmaceutical products to identify their products and distinguish them from those manufactured and sold by others.

Because of this identifying and distinguishing nature, a specific trade-mark creates certain expectations in the mind of the consumer. He assumes that:

The article bearing the trade-mark is exactly like every other article bearing such mark.

The article bearing the trade-mark always comes from the same manufacturer or from someone under his control.

The article is of standard quality or is fit for some particular purpose.

The article has certain qualities or includes certain ingredients.

It is on the fulfillment of these expectations that the maintenance and validity of the trade-mark and its protection against infringement and imitation rests.

Justice Frankfurter has well summarized the value of trade-marks in a decision of 1942:

> The protection of trade-marks is the law's recognition of the psychological function of symbols. If it is true that we live by symbols, it is no less true that we purchase goods by them. A trade-mark is a merchandising shortcut which induces a purchaser to select what he wants, or what he has been led to believe he wants. The owner of a mark exploits this human propensity by making every effort to impregnate the atmosphere of the market with the drawing power of a congenial symbol.

A good trade-mark, which serves to identify and distinguish and functions as a symbol, is a thing of great value. It may become the most important element of a business.

This is particularly true with respect to trade-marks for pharmaceutical products when the chemical titles of the products are such that, by reason of the difficulty of remembering them, pronouncing them, or writing them, they are unsuitable for practical uses. In such cases, a short, easily pronounced, easily written, and easily remembered trade-mark is what the physician, the druggist, and the customer will almost raise to the stature of the name of the product.

This may give a tremendous advantage to the owner of a trade-mark applied to a particular drug or drug product. But in a free society, this advantage is not improper, because it enables competition to bring out a similar or superior product under a different mark and leads to a lowering of prices and improvement of quality. That is why Justice Holmes could remark that "free competition is worth more to society than it costs."

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Economics of Such Trade-Marks in International Field

The economic values which trade-marks for pharmaceutical products represent are even more important in the international market. In the domestic market, the professional and nonprofessional purchasing public has additional ways by which it may exercise its choice for a particular manufacturer's product—knowledge of the high standards of a manufacturer by reputation, newspaper, magazine, or radio advertising; community experience; personal associations; and the like. In the foreign markets, trade-marks are the only means of creating and maintaining goodwill.

Postwar international restrictions affecting other trades have been less severe in the export commerce of drugs and pharmaceutical products in general. Because of their importance to public health, and the major role they play as an essential ally of scientific research and in the progress and utilization of medical science, these products may be imported more freely into foreign countries, or import licenses and foreign exchange for them are more readily given.

Trade-marks for pharmaceutical products become increasingly international. In connection with other products, there are certain arguments against standardization, particularly for big manufacturers on a decentralized pattern of operations. The fact that one and the same name may have different associations in different countries, the pitfalls presented by foreign language, the necessity to adjust slightly the composition of some products to suit national taste, historical developments of preference for particular brands—all these factors may cause manufacturers of other products to avoid uniformity of brand names for all countries.

With trade-marks for pharmaceutical products generally, the position is different. These soon find their way into the day-to-day nomenclature of medicine and pharmacy all over the world. They must of necessity represent a standard of composition and uniformity of quality. They are part of the entire identification program of a chemical or pharmaceutical manufacturer. They are regularly advertised in internationally circulated publicity media.

Another significant international angle of these trade-marks is that formulation, processing, and packaging in foreign countries by authorized licensees are becoming more and more the accepted pattern. It has now been accepted generally that the significance of a trade-mark as a guarantee of quality to the consumer depends not so much on the complete manufacture of the product in the factory where it was originally created as on the control and guarantee of the standard and quality of the product as placed on the market. The owners of pharmaceutical trade-marks find it profitable to retain the ownership of valuable trade-marks in their own hands, but to grant controlled licenses for the use of their marks by foreign manufacturers.

Bases of Protection in Foreign Countries

In this country, the concept of a trade-mark right as being derived from use has been so long with us and is so basic to our thinking that it is with great difficulty that we can accept the view that one may acquire trade-mark rights by registration only and without prior use. And yet this is the law in nearly all foreign countries, including British countries. Anyone may there register a trade-mark and acquire a statutory monopoly in it, regardless of whether he has used it before. In British countries, a bona fide intention to use the mark after registration is all that is required.

However, there is no protection for unregistered trade-marks in foreign countries, as there is under our common law. Basically, the owner of an unregistered trade-mark in the United States may obtain from the courts the same protection as the owner of a registered trade-mark. In foreign countries, this is not so. Even in British countries, an unregistered mark is protected only by the so-called passing-off action, the principle of which is definitely different from this country's common law protection. In some countries, particularly in Europe, protection is under the law of unfair competition, but the kind of proof required is much more onerous than under United States law. In Latin American countries and some other countries, an unregistered mark is not protected against infringement.

Much more serious is the difference of the law of foreign countries from this country on the question of the position of a prior user of a mark as against a prior

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applicant or registrant for such mark. In British countries and a number of civil law countries, a prior user can contest the registration of a subsequent party for the same or a similar mark. But in a number of countries, the prior user cannot overcome someone who applies subsequently for registration or at most can prevail under definite limitations.

The net result of all this is that American manufacturers or dealers in pharmaceutical products must protect their trade-marks by registration in foreign countries if they want to prevent piratical misappropriation or infringement.

Stipulations of International Conventions

For many years past, it was realized that international trade and investment is inconceivable without adequate international protection of trade-marks, and without a harmonization of the laws of the various countries on certain important aspects.

The best results in this connection were accomplished through two international acts: The International Convention for the Protection of Industrial Property, and the General Inter-American Convention for Trade-Mark and Commercial Protection.

The first was originally concluded in 1883 and has been revised successively, last in London in 1934. A new revision is scheduled for 1955. This convention contains the following principal stipulations on trade-marks:

It provides for "national treatment" of trade-marks of nationals of the contracting parties. This means that foreigners enjoy in each contracting country the same rights and protection that their law affords to their own nationals, no discrimination whatsoever being allowed and no reciprocity being required.

An applicant for a trade-mark in his home country enjoys a right of priority of six months for filing in foreign countries.

A trade-mark registered in a person's own country must be admitted to registration in the other countries, subject to certain exceptions, notwithstanding any difference in the law with respect to registrability.

The owner of a trade-mark well known in the foreign country may cancel the registration of the same or an infringing mark and suppress the use of such mark in the other countries within a period of three years or without limit of time if the subsequent party's registration was obtained by fraud.

Trade-marks may not be forfeited on account of nonuse in a contracting country except after a reasonable time and provided that the owner cannot explain nonuser for reasons beyond his control.

A trade name, as distinguished from a trade-mark, is protected regardless of registration.

False indications of origin are prohibited.

All countries are required to suppress acts of unfair competition.

For some years now, international law experts of various countries have agreed on amendments and improvements of the International Convention, and it is hoped that the following additional points of international legislation will be settled.

A period of grace of six months will be granted for renewing a registration after its expiration.

The owner of a mark may register and use in a foreign country with equal right a local translation of his mark.

Unauthorized registrations by an agent or representative of the owner of a mark shall inure to the latter's benefit.

Assignment of foreign trade-marks without the good will may be permitted.

Licensing of trade-marks will be freely permitted.

Marks of great reputation will be protected against their use even on dissimilar products.

The General Inter-American Convention of 1929 is the latest of a series of Pan American conventions on the subject of trade-marks. Many of its provisions are analogous to those of the International Convention. In addition, however, it provides for the protection of the first user against an infringing applicant or registrant at any time or even by showing, in the absence of prior use in the foreign country, that the applicant or registrant had knowledge of the prior owner's right. It also stipulates that unauthorized registration of a trade-mark by an agent or representative of the owner inures to the benefit of the latter and must be transferred to the owner.

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The only bad thing is that this Inter-American Convention has been ratified by ten American republics only and the other eleven are not party to it.

On the contrary, the International Convention for the Protection of Industrial Property has been ratified and is in effect among 47 countries, which include practically the whole of Europe (and its colonies) (outside Soviet Russia), most of the British Commonwealth, Japan, and six American Republics: Brazil, Cuba, Dominican Republic, Haiti, Mexico, and the United States.

Piracy and Infringement

Trade-marks for pharmaceutical products, like any other marks, are exposed to piracy and infringement.

Piracy is the misappropriation of a trade-mark with the pirate's knowledge of the prior ownership and use of such trade-mark by its true proprietor. This is particularly true of pharmaceutical marks in foreign countries, and is explained by the fact that so many of them are new and adopted for new products. It is a particular feature of the American picture that the manufacturer of a new drug or drug product is naturally led to announce it, and with it the trade-mark identifying it, to the American market by publicity in national American magazines. This is natural, because the manufacturer thinks primarily of the American market of 165,000,000 people.

What happens, however, is that American national magazines have an international circulation and distribution and the announcement of the new product and its trade-mark is made quickly known to many in foreign countries. Pirates will then rush to apply for registration of such trade-mark in their name. Their aim is to hold up the foreign manufacturer and demand tribute for the use of the trade-mark, or at the very least to obtain exclusive distribution rights in their particular country.

Many American manufacturers had sad experiences with such happenings in recent years. The only protection against this is to place oneself in the position where there would be a legal basis for succeeding against such pirates. In countries where prior user gives title to the trade-mark, the owner of a trade-mark for pharmaceutical products must establish technical user in such countries. On the other hand, where ownership in a trade-mark is acquired only by registration, the trade-mark owner must apply for registration without delay.

Infringement of trade-marks for pharmaceutical products is a permanent problem. As Dean Wigmore said: "The fact is, no commercial business grows into healthy largeness without becoming soon the victim of the business parasite . . . who attacks and seeks to absorb the unearned benefit of the other man's labor and money."

Every successful trade-mark is exposed to the danger of imitation and infringement. The only way to protect such a trade-mark is to object against and attack every imitation. There are two philosophies one can choose about it. One is to be very cautious and attack only imitations against which one may have good assurance of success. The result then will be that the owner will lose very few cases but at the same time will finish by having a narrow scope of protection for his trade-mark. The other philosophy is to be daring and sensitive about imitations and attack any imitation of one's trade-mark which comes close to it. The net result of this will be that one may lose many cases but he will finish by getting a broad boundary line round his trade-mark and a large scope of protection for it.

Unfair Competition Problems

Here is a subject for which there is international consciousness but not always adequate law and procedure. The International Convention for the Protection of Industrial Property gave an international definition to the concept in 1925 after some preliminary work of the Economic Committee of the League of Nations. It calls unfair competition "any act of competition contrary to honest usages in industrial or commercial transactions." Honesty, then, in the conduct of businesses competing in the market place is what we are after. In the United States we go to the equity courts for relief in unfair competition cases and a great judge has said that "the invocation of equity rests more vitally upon the unfairness rather than actual market competition between the parties."

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The concept of unfair competition grew and developed essentially to meet unfair conduct in business competition outside the more or less fixed technical boundaries of the specialized laws of industrial property rights. It expanded from small beginnings to a broader scope to keep pace with the protean transformations of fraud or acts which strike the ordinary, right-minded person as unfair, unsportsmanlike, and immoral. And so the law of unfair competition gradually has been conceived, not as a separate compartment of the law of industrial property of fixed or narrow boundaries, but rather as the all-inclusive basic concept of which the specialized laws on trade-marks, trade names, geographical indications of origin, mismarking, etc., are but species of a genus. Correctly then a great judge in the United States, Justice Oliver Wendell Holmes, said that: "The word 'property' as applied to trade-marks . . . is an unanalyzed expression of certain secondary consequences of the primary fact that the law makes some rudimentary requirements of good faith" (*Dupont* vs. *Masland*, 244 U. S. 100, 102).

Adequate protection against unfair competition involves two things: a broad concept of unfair competition with the emphasis on the unfairness rather than on the competition part of the term, and effective remedies against it. How far have the various countries in the world given effect to these two requirements? A most varied condition of law exists today:

A number of countries have no law on unfair competition at all, either by statute or by court decisions, or have a most rudimentary law applicable only to situations of pure fraud.

A number of countries have enacted legislation, but such legislation is directed to certain limited specific acts of unfair competition, such as false advertising, interference with contracts with employees, fraudulent disparagement, fraudulent acts of confusion with the name of another, misuse of business secrets, and the like, but without an all-inclusive prohibition of acts contrary to honest practices.

A number of countries have a special statute of unfair competition with a broad prohibition and also a specific enumeration of specific acts of unfair competition.

Lastly, other countries have no legislation but have developed a full body of unfair competition law by judicial construction of a general provision of the civil code or of general principles of common law.

With respect to remedies, there is equal divergence. In some countries, penal action only is provided, which is difficult of application as it involves an inquiry into the existence of an element of fraud. In others the remedy is an ordinary civil action which is usually a long drawn out and costly proceeding from which businessmen are usually deterred. In few countries is a speedy remedy such as preliminary injunction provided, which can bring about, by an initial judicial pronouncement and subsequent negotiations between the parties, a quick discontinuance of the objectionable practices. In very few countries a recourse is also available to a special Committee on Competition of a general trade organization which permits an opinion to be given in advance of judicial recourse and which may suffice to bring an end to unfair practices.

Particular attention may be given to the General Inter-American Convention for Trade-Mark and Commercial Protection signed by the American republics in Washington in 1929 which contains in Chapter IV a code of international legislation on the subject. This chapter of the convention has been incorporated in the law of the United States through the provisions of Section 44 [subsections (*h*) and (*i*)] of the Lanham Trade-Marks Act of 1946.

Generic or Nonproprietary Names

A general rule of law in all countries is that no trade-mark rights may be obtained or claimed in respect to generic names or names which describe the genus or kind of products and which shall be common to the trade. To allow such generic names to be monopolized would be an intolerable condition of things. For pharmaceutical products two problems in this connection require particular attention:

First, unscrupulous persons, in noncommon law countries particularly, attempt to register generic names so as to prevent legitimate manufacturers and traders from using them in connection with pharmaceutical products. It is true that in many cases the claim by such persons may be defeated but it takes a court action to do this if they obtain registration. But in many cases where new generic or non-

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proprietary names are adopted by pharmaceutical manufacturers for newly invented or formulated products, the foreign patent office or courts may not admit that such a name is generic in their country since it may not have been actually used by the trade in that country. This has led respectable and leading manufacturers in the United States to register in foreign countries the generic names used in conjunction with their marks, not for the purpose of monopolizing such names but in order to prevent pirates from attempting to register to the determent of the legitimate trade. However, this action arouses the suspicion of competitors and confusion and conflict ensues.

To show how bad the situation is, the following list of pharmaceutical generic or descriptive words was filed for registration in foreign countries in 1953 alone and which American manufacturers or associations in this country, such as The Proprietary Association, or American Pharmaceutical Manufacturers' Association, Inc., had to oppose:

Cortisone	Isonizid
Penicillin	Codeine
Intrarectal	Hospital
Histamine	Testosterone
Chlorophyllin	Acetopyrine
Chlorophyll	Penicilina
Calcium	Amphetamine
Antacid	Streptomycin
Salicymide	Carbomycin
Anti Microbe	Progesterone
Hydrolysate	B 12
Vegetable Compound	Infantile Medicine Therapy
Vitamin	Pediatrics
Chloro Vitamin Dragees	Medical
Amino Acid	B-Complex
Aminophylline	Pepsin
Vaccine Solvent	Hematinic Lime
Vitamin Drops	Powdered
Hydrochlorophyl	Glycol
Phenothiazine	Antibiotic
Digitalin	

How to solve this problem is a real puzzle.

Related to this problem is another—the activity of the World Health Organization on nonproprietary names. On the basis of resolutions and rules of procedure adopted by its Executive Board and recommendations of a Committee of Experts consisting of medical men, it proceeded two years ago to designate certain names as nonproprietary names for which no trade-mark rights could be claimed. These were communicated to the member states.

As the impact of this work began to be felt, severe criticism was voiced. It was claimed that WHO, through this program, tended to destroy legitimate trade-mark rights by adopting and publicizing certain names as generic names when they were really private trade-marks or confusingly similar to such marks. No adequate system of consultation and hearing of interested parties was practised.

As a result of this criticism, the whole program was re-examined at the Sixth World Assembly in Geneva in May 1953, and new rules of procedure were adopted entitled "Procedure for the Selection of Recommended International Nonproprietary Names for Drugs Moving in International Commerce."

Under these new rules, proposals for nonprietary names will be submitted directly to the Director-General of World Health Organization. These will be referred to the Subcommittee on Nonproprietary Names of the Expert Advisory Panel on the International Pharmacopoeia. This subcommittee will consider the names proposed for a particular substance and will make its recommendations to the Secretariat. Then notice of this recommendation is to be published in the *Chronicle* of the World Health Organization and sent by letter to the member states, to the pharmacopoeial commissions, and other bodies designated by the states. A six-month period is allowed for filing of comments on or objections to the proposed names. Any firm or individual interested may file such. When a formal objection has been filed, WHO may either reconsider the proposed name or use its good offices

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to attempt to obtain withdrawal of the objection. While a formal objection exists on record, a name will not be selected by WHO as a "recommended international non-proprietary name."

Thus, while WHO does not make trade-mark searches when it publishes a proposed name, the provision for formal objection safeguards rights in previously adopted trade-marks. Thus, the whole program now has a voluntary character and avoids the impairment or destruction of valuable trade-mark rights.

The use on a world-wide basis of a single common or generic name for a drug is highly desirable. It must be sought in a manner which does not conflict with existing trade-marks. Hence, those who claim such rights must be heard.

On the other hand, this may assist primarily against "pirates" who attempt to register as trade-marks words which are obviously and admittedly generic or descriptive. The work of WHO may assist in this respect.

But ultimately the problem involves national action in each state. In view of its voluntary character, the procedure of WHO may not succeed. Perhaps the solution is through an appropriate stipulation in the International Convention for the Protection of Industrial Property establishing a procedure that will be binding on all member countries.

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Transformation of Pharmaceutical Trade-Marks into Generic Names

A very important problem which arises with respect to pharmaceutical trade-marks used in connection with a patented product or process is what happens to such marks when the patent expires. The present doctrine of our U. S. courts is that the expiration of a patent is only of some evidential value in determining whether or not the name of the article made under the patent has become descriptive.

In British countries under the law prior to 1938 the law was settled that when an article has been originally manufactured under a patent, the name by which the article was known by the public when the patent was in force became open to the public immediately on the expiration of the patent.

The trade-mark law was changed in Great Britain in 1938 and subsequently in most of the British Commonwealth, and the previous severity of the rule was moderated. The law there now is that the registration of such a mark remains effective in any case for a period of two years after the patent has lapsed and thereafter continues in force unless it is proved that the mark is the only practicable name or description of the article or substance. This change of the law concerns only registered trade-marks. With respect to unregistered trade-marks, the law is as it was prior to 1938. This emphasizes from one further point of view the great usefulness of registration of pharmaceutical trade-marks in British countries.

Under the British rule, both the old and the new, the position is the same not only when the product is made under a patent, but also when the trade-mark has been established as the only name or description of the article or substance in question.

For this reason, in British countries as in our country, the manufacturer of a new product bearing a new trade-mark must also create and give to the public a generic name for the product or substance so that it may always be possible to show that the trade-mark is not the only practicable name or description of the article or substance in question.

In civil law countries—such as Germany, France, Italy, etc.—there is no similar doctrine. The expiration of a patent has no influence whatsoever on the validity of a trade-mark with respect to a product made under the patent. Therefore, there is no legal necessity for the owner of such a trade-mark to devise and use a generic name for the product in question independently of the trade-mark itself. European pharmaceutical manufacturers consider it commercially inadvisable to use such a generic name because it enables competitors to come out with a similar product under a different mark but using the same generic word.

The legal position in this respect in civil law countries is tied up with the much readier acceptance in these countries of factual monopolies and their allergic reaction against our common law and statutory theory of freedom of competition and unlawfulness of restraints of trade.

Relating to the same problem is the general legal theory of the transformation of a trade-mark into a generic term. Under French, Swiss, German, and Italian

law, and generally in other civil law countries, a trade-mark most rarely and exceptionally falls into the public domain no matter how far such mark may actually become the name of the product in the eyes of the general public. In France particularly, a trade-mark never falls in the public domain, regardless of whether the owner has tolerated its use by others. Only an affirmative act on his part dedicating the mark to the public will cause the loss of the trade-mark. In Switzerland and Germany the courts insist on complete transformation of a mark to a generic name to the extent where the memory of the trade-mark as a trade-mark has completely vanished. Even though no current technical name exists for the product in question and the mark is the only possible designation for it, the courts impose on the interested persons or competitors the duty to create themselves another name which will not infringe the trade-mark.

Therefore, registered trade-marks are much more valuable rights in civil law countries than in the United States or British countries in the sense that once property in a trade-mark has been acquired by registration it is extremely difficult for such a trade-mark to be lost, unless the owner is determined to abandon it and does affirmatively proceed to do so.

Notwithstanding this, however, the wise practice is to use even in foreign countries a generic name in conjunction with pharmaceutical trade-marks because the scope of protection of such a trade-mark will then be much broader and its protection against imitations much more secure.

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Licensing Arrangements

Perhaps at no time in the past has the licensing by American pharmaceutical manufacturers of qualified firms in foreign countries to formulate, process, package in dosage form, or to effect complete manufacture and use the trade-marks of the American manufacturers been so active as in recent years. In this respect the largest program of international cooperation and joint venture in the broad sense is being observed. The causes, of course, are many—import restrictions, foreign exchange difficulties, a desire to reduce costs and prices for foreign markets, or plain cooperative undertakings for mutual benefits. Sometimes the American manufacturer exports the drug or drug product in bulk and has the foreign connection package the article in dosage form. Sometimes he exports the main ingredient and relies on the foreign firm, under his control, to obtain the supplementary ingredients locally. Sometimes the foreign firm having first class laboratories of its own makes the entire product.

In all these cases, the arrangements provide that the marketed products will be labeled and sold under the American manufacturer's trade-marks. This is an eminently sound requirement on the part of the American manufacturer. Because once he has given to the foreign firm his know-how, formulas, specifications, and technical instructions, the only way by which he can hold on to the foreign good will is to require that the product be marketed under his mark. Then, if the arrangement should for any reason be terminated or cancelled, the American manufacturer will continue to own his trade-mark and export the product from the United States or make arrangements with another firm, at the same time benefiting from the enlarged good will appurtenant to the trade-mark developed for his benefit by the foreign licensee.

However, license arrangements under the law of some countries involve delicate points and may entail serious risks for the trade-mark and accordingly should be very carefully prepared. Particularly, the law is not uniform as to the permissibility of licensing of trade-marks or makes specific requirements for its validity.

The various countries in the world may in this connection be classified into various groups:

Countries where a trade-mark may be licensed only through the procedure of the so-called registered user. These are most of the British countries today.

Countries in which a trade-mark license must be recorded in the Patent Office.

Countries in which a trade-mark license is unlawful and may invalidate the trade-mark.

Countries in which a license, though generally not lawful, may nevertheless be tolerated under specific conditions and terms.

Countries in which a trade-mark license is entirely lawful and is not subject to any conditions or requirements.

In any case, under any license arrangement, care must be taken to avoid any deception of the public as to the origin or as to the person who is in the last resort responsible for the standard and quality of the products as placed on the market. Therefore, truthful and complete marking and labeling are essential for the preservation of the trade-marks on pharmaceutical products and the safeguarding of the valuable good will attached to them.

The American manufacturers who are anxious to create and maintain a foreign market for their products are probably more fully aware of the necessity of following a policy which is in complete accord with the common good. They are guided not only by a feeling of social responsibility but also by a self-enlightened interest in controlling strictly the standards of quality and uniformity of the products sold in foreign countries under their trade-marks. In the last resort a trade-mark is the natural offspring of the buyer's market, and the ultimate verdict of the consumer who chooses carefully and decides freely. This verdict is crushing and final against the producer who fails in his responsibility to the public.

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