REVIEW ARTICLE

DISCOVERIES IN THERAPEUTICS*

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THE attitude of the medical profession towards drugs has undergone a remarkable change during the last 50 years. At the end of the 19th century it had become clear that a large proportion of the traditional remedies had no real effect on the course of disease. Sir Henry Dale[1] (1943) has given a striking picture of his disappointment as a medical student when he realised the position. Quinine was effective against malaria, ipecacuanha against dysentery and mercury against syphilis. Digitalis, morphine, cocaine, bromides, salicylates, and general anæsthetics had their uses but their effects were palliative rather than curative and although there were 857 drugs in the British Pharmacopœia most of the others seemed to be comparatively useless.

Great changes have occurred since then. A large number of powerful new drugs have been introduced and a large number of old drugs have been transformed into useful therapeutic tools. The physician of to-day can do very much more for his patients than the physician of 50 years ago and if progress continues at the present rate the physician of to-morrow will be able to do much more still. From the point of view of the patient this kind of progress is of supreme importance. The object of this review is to analyse the methods by which new remedies are discovered, in the hope that progress in therapeutics may be accelerated.

A complete account of the methods by which all modern remedies were discovered would be a vast task, and it has been necessary for me to prepare a select list of important remedies for discussion. The list was originally based on the index of the "Textbook of Medical Treatment" by Dunlop, Davidson and McNee,[2] but has been modified. It includes about 200 drugs all of which have some claim to be separate and effective remedies. This list is, of course, an arbitrary one, and can be criticised in detail, but it probably contains most of the really potent drugs introduced before 1950.

A study of this list confirms the impression that therapeutics is advancing to-day more rapidly than it has ever advanced before. The number of remedies in the select list introduced in the 50 years between 1900 and 1950 is equal to the number introduced before that time.

It may perhaps seem surprising that so large a proportion of the drugs in use to-day were already known in 1900. Quite a number of really effective remedies were first used at a very early date, but for long ages their value was obscured by the fact that they were buried in long lists of other remedies, most of which were quite useless. The modern pharmacopœia is a much more select and critical document than its predecessors. Many useless drugs have been cast out, but many other old drugs have been made into useful remedies in the light of modern knowledge.

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Some of the remedies still in use to-day were discovered before the dawn of recorded time and the real history of the beginnings of pharmacology will never be written. We shall never know who it was that first discovered the interesting pharmacological effects of alcohol. Some of the virtues of milk and honey and salt and sulphur were known from the earliest times.

The earliest recorded pharmacological experiments were carried out in 2700 B.C. by the emperor Shen Lung of China, who tasted all the drugs in the pharmacopœia of his day and classified them accordingly. Ma Huang was classified as a medium drug and when its active principle was isolated nearly 4000 years later it was called ephedrine. It had been used for hundreds of years in China as a stimulant of the circulation, as a diaphoretic, as an antipyretic and a sedative in coughs. Modern observations confirm that it is effective in most of these conditions. Ephedrine was isolated in 1887 and for the next 30 years it provided a happy hunting ground for the chemists. Its effect on the pupil was likened to that of the sympathetic in 1892 before adrenaline was discovered. In 1917 its pharmacology was investigated again by two Japanese workers who showed that it had sympathomimetic effects like its chemical relative adrenaline. Chen and Schmidt isolated ephedrine and showed that it acted like adrenaline before they discovered that these facts were already known. However, their paper, published in 1924, had a very important effect because it was written in English. It is interesting that fundamental pharmacological facts about ephedrine were discovered three separate and independent times before its use became general.

Two other drugs which we owe to ancient China are tea and rhubarb, both of which were known to Shen Lung.

The Ebers papyrus was written in Egypt about the year 1550 B.C. It is a textbook of therapeutics based partly on the experience of the author himself and partly on the writings of earlier authors[3,4]. It contains many interesting and true observations particularly with regard to purgatives; it has always been easy to make clinical observations on the action of purgatives.

The papyrus recommends castor oil, figs, manna, senna and colocynth as purgatives, and plants containing tannin as astringents, pomegranate for round worms and liver for night blindness. This last remedy, which presumably owed its action to vitamin A, is distinguished by a special note that it is really excellent. Copper, antimony, hyoscyamus and iron are also mentioned. Over a dozen of the drugs on my list are included, but many of the drugs mentioned in this papyrus have not been identified and the Egyptians may perhaps have known of even more of our modern remedies than these calculations suggest.

The Greeks inherited many drugs from Egypt but added a large number of their own. Theophrastus, who was born in 380 B.C., was a pupil of Aristotle and his book on materia medica probably represents Aristotle's information on the subject. It included opium, mustard plasters and tar for the skin, filix mas for tapeworms, and aloes as a purgative.

Dioscorides wrote a comprehensive treatise on materia medica in the first century A.D. which contains references to many other drugs used

to-day, including santonin for worms, alkaline diuretics for œdema, gentian, chalk, mercury and lead salts and clay poultices—which may be regarded as the origin of the kaolin poultice. The fact that goitre depends on the water supply has been known for at least 2000 years, but the first clear reference to the use of a remedy rich in iodine in the treatment of goitre is in the writings of Roger of Salerno who recommended burnt sponge for this purpose in 1170 A.D.

The schools of medicine which flourished in Mohammedan cities in Persia, in Mesopotamia and in Spain in the 10th and 11th centuries, and which used the Arabic language, preserved the ancient medical lore of Egypt and Greece for posterity, and introduced four of the drugs in my select list. They get the credit for introducing camphor from Malay and China. Colchicum had been described by Dioscorides as a poison; the Arabic writers recommended it for gout. They also introduced silver and gold into medicine, though not for the same diseases as Dunlop, Davidson and McNee. They used silver for auricular fibrillation. In later years, it was given to lunatics because it was associated in men's minds with the moon, which was well known to control the actions of lunatics. The local use of silver dates from the 16th century, when it was used as a hair dye. It was first used as a caustic in the 17th century and its antiseptic action was discovered by Neisser and Behring in the 1880's. The Arabs also used potable gold as an elixir of life.

Between the years 1300 and 1850 progress in therapeutics was still fairly slow. The discovery of America led to the introduction of cinchona for malaria, ipecacuanha for dysentery, chenopodium for worms, lobelia for asthma and quassia as a bitter. During this period Dutch sailors discovered the value of lemons in the treatment of scurvy, and magnesium sulphate was first described as the active purgative in the spring water which had become a fashionable drink at Epsom.

Digitalis was an old folk remedy grown by Gerard and Parkinson and Salmon and other herbalists and used for scrofula (that is tuberculous glands) and for local application to sores and for epilepsy. Its real value was established by Dr. Withering of Birmingham in a book published in 1785[5]. He described his results with foxglove on 100 cases and noted its effect on the heart and as a diuretic. He met with a lot of opposition, but did succeed in establishing digitalis as a valuable remedy.

Oil of eucalyptus was first used in 1790 by the early settlers in Australia as a substitute for oil of peppermint in the treatment of wind and colic.

Salicylates were first obtained from willow bark (Salix), and willow bark was introduced into medicine in the first place as a substitute for cinchona bark which previously had become known as a substitute for the bark used in preparing balsam of Peru. Salicylic acid was first synthesised commercially from phenol in 1874 and within two years it was established as an antiseptic, antipyretic and antirheumatic, and salicylates came into general use.

The history of ergot is complicated but interesting[6]. Its use by midwives was described in 1582, but it was not introduced into official medicine until 1808. In the early years of the 20th century extracts of ergot were

found to contain a large number of active drugs. They were the first natural source of histamine, acetylcholine, and a number of other interesting substances which are widely distributed in nature, but they also contain specific alkaloids which are found nowhere else. In 1932 ergotoxine had been on the market for 25 years, and ergotamine for about 10 years. These specific alkaloids were generally thought to be the real active principles, but, in spite of repeated efforts by the pharmacologists, it had been so far impossible to persuade the clinicians to produce good evidence of their real value. The official British extract of ergot contained no ergotoxine and no ergotamine; some people said it was nevertheless effective, but opinion was divided. The discovery of the real active principle was due to the application of a pharmacological technique to a human patient. Chassar Moir (1932) recorded the human uterine contractions after childbirth and showed that ergotoxine and ergotamine were both active in stimulating the uterus, but he also found that liquid extracts containing neither of these substances were even more effective and quicker in action. This work provided a test for the most important active substance, which was soon isolated by chemists in 3 different countries and became known as ergometrine.

TABLE I

DRUGS INTRODUCED BEFORE 1850

PREHISTORIC—Water, alcohol, milk, salt, turpentine.
EARLY CHINA—Caffeine, rhubarb, ephedrine.
EGYPT, 1550 B.C.—Glucose (honey), olive oil, bran poultice, castor oil, senna, tannin (for diarrhœa), liver for night blindness, bone marrow, atropine (hyoscyamus), iron for anaemia, copper, antimony, zinc.
THEOPHRASTUS, 300 B.C.—Filix mas for worms, opium, aloes, mustard plaster, tar.
DIOSCORIDES, 78 A.D.—Santonin, clay poultice, gentian, alkaline diuretics, chalk, mercury, lead, lanoline.
12TH CENTURY—Burnt sponge for goitre, colchicum for gout, camphor, gold, silver, berberine.
16TH CENTURY—Lemons for scurvy, croton oil, chaulmoogra for leprosy.
17TH CENTURY—Blood transfusion, Epsom salt, nux vomica, cinchona, ipecac, chenopodium.
18TH CENTURY—Digitalis, willow, vaccination, oxygen, charcoal, menthol, quassia, eucalyptus.
1800-1850—Ergot, cod liver oil, lobelia, nitrous oxide, ether, chloroform.

The most important pharmacological event in the first half of the 19th century was the introduction of general anæsthesia[7]. The anæsthetic action of nitrous oxide was discovered by Humphrey Davy. He published his results in 1800 when he was 22 years old[8]. His book is a model for all pharmacologists to copy. He described the chemical properties of nitrous oxide and its effects on a wide variety of animals. He showed that pure nitrous oxide caused death and that for anæsthesia it was necessary to mix oxygen with it. He repeatedly anæsthetised himself with it and recommended that it should be used in surgical operations. In 1844 Horace Wells, a dentist of Hartford, Connecticutt, used the gas for the extraction of teeth, but nitrous oxide was not finally introduced till 1863.

Meanwhile, the intoxicating effects of ether were fairly well known. They had been compared with those of nitrous oxide in 1818 in a note attributed to Michael Faraday. Ether was first used at an operation in America. The chief credit for its introduction is due to Morton of Boston who gave a successful demonstration on October 16, 1846, and within a few months ether was in general use all over the world. Chloroform was first used as a general anæsthetic by Sir James Simpson in

Edinburgh on November 16, 1847—so that all these important general anæsthetics were first used in medicine within a few years of one another. Chloroform, like ether, was generally adopted quite rapidly.

It was a little earlier than this that there appeared the first signs of the scientific upheaval which has revolutionised therapeutics. During this time the fundamental facts of physics and chemistry and physiology were

TABLE II

DRUGS INTRODUCED SINCE 1850

British Commonwealth

1850	Permanganates, bromides.
1860	Eserine, apomorphine, phenol, amyl nitrite.
1870	Nitroglycerine.
1890	Typhoid vaccine, thyroid, strophanthus, hydrogen peroxide.
1900	Pituitary extract, carbon dioxide.
1910	Pollen, gum acacia, acriflavine, eusol, chloramine-T.
1920	Insulin, parathyroid, peptone, ammonium chloride, cyclopropane.
1930	Alum toxoid, typhoid serum, Russell viper venom, magnesium trisilicate, diamidines, stilboestrol, mandelic acid.
1940	Antibiotics, cyanocobalamin, dyflos, dimercaprol, mutagens, mephenesin, methonium drugs.

U.S.A.

1880	Liquid paraffin.
1900	Adrenaline.
1910	Dysentery serum, lactose, carotene.
1920	Scarlet fever antitoxin, liver, vitamin E, nicotinic acid, carbon tetrachloride, tryparsamide, iodophthalein, hexylresorcinol.
1930	Progesterone, helium, riboflavin, neostigmine, phenytoin, amphetamine, dinitrophenol.
1940	Other antibiotics, dicoumarol, hyaluronidase, folic acid, cyanocobalamin, antituberculosis drugs, nalorphine, antithyroid drugs, dibenamine, chlormethine, dimethylcarbamazine.

German speaking countries

1860	Trichloroacetic acid, chloral hydrate.
1880	Cocaine, ichthyol, creosote, bee venom, formalin, betanaphthol, paraldehyde, iodoform, phenazone, phenacetin, methylene blue, gentian violet.
1890	Diphtheria antitoxin, tetanus antitoxin, urea, X-rays, aspirin, amidopyrin, hexamine, orthocaine.
1900	Kaolin, barbiturates, procaine, cinchophen, arsphenamine.
1910	Phenylhydrazine, phenolphthalein.
1920	Gonadotrophin, suramin, pamaquin, chiniofon, mersalyl, leptazol, niketamide, bromethol.
1930	Œstrin therapy, sulphonamides, mepacrine, carbachol, dihydrotachysterol.
1940	Dihydroergotamine, isoprenaline, methadone, leucanthone, caramiphen, *p*-aminosalicylic acid, lysergic acid diethylamide

The rest of the world

1850	Chyrsarobin, curare.
1870	Thymol.
1880	Rabies vaccine.
1890	Cholera vaccine, anthrax serum, vitamin B, thallium.
1900	Whooping cough vaccine, radium, trypan blue.
1910	Benzyl benzoate.
1920	Bismuth, thiosulphate, acetarsol.
1930	Vitamin K, vitamin P, antiadrenalines.
1940	Antihistamines, synthetic curares, disulfiram.

established. The whole technique of scientific experiment and scientific logic was built up into a powerful weapon which has been used to devise new methods of preserving human life, as well as new methods of destroying it.

This has led to a great increase in the rate of discovery of new remedies. During the 17th and 18th centuries the drugs on my list were being introduced at the rate of about 5 per century, or one drug every 20 years. In the 19th century the rate of discovery rose rapidly and between 1890 and 1900, 16 of these remedies were introduced or 1.6 remedies per year. Since then the rate has risen still further to a maximum of 2.7 remedies per

year, but the rise has not been a steady one. The recent data are divided into 4 groups, according to whether the remedy was first introduced in the British Empire or in the U.S.A. or in German-speaking countries or in the rest of the world. This has involved some arbitrary decisions, and the assumption has been made that, with a few obvious exceptions, the nationality of authors was the same as that of the country in which their results were published. All the German-speaking countries are classified together because it would be difficult to disentangle them, but most of the remedies thus classed together were actually discovered in Germany.

The first thing to be seen in this list is that the British have not been doing so badly after all. Since 1910 the British have introduced 24 of these remedies, the Americans 29, and the German-speaking countries 22.

The Americans introduced the general anæsthetics ether and nitrous oxide in the 1840's, but after that they get credit for nothing more until 1900 except liquid paraffin. The Americans did not really start introducing new remedies until the first world war was over, but since then they have shot ahead of all other nations.

In the years 1850–1880, 12 of these remedies were introduced. Permanganates were introduced by Condy in 1857 and bromides were first used in the treatment of epilepsy at about the same time.

Curare had been studied for half a century before Claude Bernard[9] showed in 1856 that it acted by stopping the transmission of impulses from motor nerves to voluntary muscles. Quite recently anæsthetists have started using curare to increase muscular relaxation during operations. It is interesting to enquire why over 80 years elapsed before this application of Claude Bernard's work became a practical proposition. Curare was first used clinically in 1859 and during the next 40 years it was given to patients in France suffering from rabies, tetanus, epilepsy and chorea. Interest in the subject then appears to have lapsed, probably because the drug was difficult to get, variable in potency, and liable to contain toxic impurities. In 1930–1935 Ranyard West[10] did much to attract attention to curare and tested its use in various clinical conditions. He helped to arouse the interest of Dr. Harold King[11] who isolated the alkaloid, which is known as tubocurarine, and established its chemical structure. In 1940 Bennett[12] injected curare to control the convulsions of patients undergoing treatment with convulsant drugs, using an extract known as intocostrin and this was used by Griffith and Johnson[13] as an aid to muscular relaxation during anæsthesia. The pure alkaloid tubocurarine is also effective and has the advantage that its composition is certain to be constant. Recent progress on curare has been due to the skill of the pharmacologists and chemists, but it is doubtful if they would have worked in this field if they had not been encouraged by the enthusiasm of the clinicians.

The ordeal beans used in the trials of witches at Calabar on the coast of Nigeria were first made known in Europe in 1840. Most of the fundamental work on this poison was done in Edinburgh where Professor Christison ate the beans, and survived because he took an emetic[14]. His assistant, Thomas Fraser, analysed their effect with great care[15], and isolated their active principle, which he called eserine. He demonstrated its

constrictor effect on the pupil and first used it for this effect. This substance has played a very important part in the development of physiological knowledge, since it was found by Loewi and Navratil[16] in 1926 to protect acetylcholine from the enzyme which destroys it. Without eserine our knowledge of the neuromuscular transmission of nervous impulses would be much less complete than it is to-day. The chemical structure of eserine was established by the Stedmans who synthesised many substances with similar actions. This work led to the introduction of neostigmine in 1931, but the latter substance was actually first prepared and used in America and this drug has been allotted to the U.S.A. The most interesting use of neostigmine is in the treatment of myasthenia gravis in which it temporarily cures the impaired conduction at the nerve ending. This discovery depended upon Claude Bernard's work on curare. It was shown by Pal[17] that the paralysing action of curare was antagonised by eserine. Clinical observations on myasthenia during the early part of this century led to the conclusion that the symptoms of this disease were similar to the effects of curare. These facts were the logical basis of the discovery in 1934 of the effect of eserine on myasthenia by Dr. Mary Walker[18].

In the 1880's therapeutics developed in two important directions. There was a sudden great output of synthetic drugs in Germany and immunology was established by the work of Louis Pasteur[19] on rabies. New chemical compounds were made with the deliberate object of discovering new remedies and were selected from among a host of allied substances, by experiments on man, or more usually on other animals. Organic chemistry was beginning to stretch itself, and to realise that a new technique for the fixing of methyl groups to a particular site in a molecule could be applied without much trouble to the fixing of dozens of alternative groups to the same site. Chemists were pleased to find that substances produced in this way could be handed over to pharmacologists, and that the pharmacologists would say that some were inactive and some were too toxic and that out of each series there was usually one that was better than all the others and worth trying on patients. Phenacetin is an example of a drug discovered in this way. It was chosen from a series of homologues containing groups of different sizes. The higher members of the series were inactive and the lower members were too toxic. The choice was made by pharmacological experiments and it has stood the test of time. A number of allied substances were made and marketed, but phenacetin has been the most successful.

Rabies vaccine was introduced by Pasteur in 1880. Vaccination against smallpox had been practised for centuries, and its value had been established as a scientific fact by Edward Jenner in 1798. Pasteur's discovery of the value of rabies vaccine was due to the accident that while he was away on a holiday, preparations of the virus of chicken cholera which he had left in his laboratory lost their virulence, so that the chickens into which he injected them did not get chicken cholera, but did become immune to this disease. This showed Pasteur that it was possible to confer immunity without exposing the patient to the danger of the disease. It needed great

courage to apply this knowledge to the treatment of rabies in man, but the success of Pasteur's experiments led directly to much other fruitful work in immunology.

In the 1890's the synthetic drug industry was flourishing in Germany but nowhere else. In these years great advances were also made in immunology. Behring and Kitasato announced the discovery of an effective tetanus antitoxin prepared by immunising animals with the exotoxin liberated into culture media by the tetanus bacillus, and a week later the same authors announced that diphtheria antitoxin could be made by the same method. Effective vaccines were made by Almroth Wright for typhoid, and by Haffkine for cholera. All these discoveries have played an important part in the world.

The same period saw the first successful use of hormones in therapy. Dr. George Murray[20] of Newcastle, made a glycerol extract of sheep's thyroid which he injected into a patient with myxœdema with good results. This was a logical thing to do, since it had just been proved that myxœdema was due to lack of thyroid. But it was also a brave thing to do and was the beginning of an important branch of therapeutics.

Another discovery of this period was the use of strophanthus in heart disease. This was the outcome of careful researches in Edinburgh by Sir Thomas Fraser[21] on the pharmacology of poisoned arrows.

The first 20 years of the present century were not particularly fruitful. The pressor effects of extracts of the adrenal medulla and of the pituitary posterior lobe were discovered by Oliver and Schafer[22] about 1895 in University College, London, but the credit for adrenaline goes to the U.S.A. because it was there that it was first isolated, and it was there that it was first used therapeutically. Germany still led the world in the synthetic drug industry. Only two synthetic drugs in the list were introduced outside Germany in the first ten years of the century. Phenolphthalein was used as an indicator of *p*H for 30 years before its purgative action was accidentally discovered[23]. Trypan blue was first used as a wool dye. Its chemotherapeutic action was discovered in France[24]. In these same years the Germans introduced the barbiturates as hypnotics[25], procaine as a local anæsthetic[26], cinchophen for gout[27], and arsphenamine (or salvarsan) for syphilis[28]—four big achievements.

The work of Ehrlich which led to the introduction of arsphenamine established the importance of the experimental study of the treatment of infections. Ehrlich investigated the effects of a long series of compounds on mice infected with various protozoa and so selected drugs which were active without being too toxic. He used the word chemotherapy to describe his work, and this word now means the study of the effects of drugs on infected animals, whether the infective agent is a protozoon or a bacterium or a worm.

The period of the first world war was not very fruitful. Judging by my list the war stimulated the British more than it stimulated anyone else. Their war effort included the first use of gum acacia in the treatment of shock[29], and of acriflavine[30], eusol and chloramine-T[31], all of which are effective disinfectants for wounds.

The most dramatic achievement of the 1920's was the introduction of insulin in 1923. This was the culmination of a long period of patient work on the physiology of the pancreas[32]. It was already known that diabetes mellitus was due to deficiency of a hormone liberated by the pancreas. This hormone was first called insuline in 1909 and many people had made extracts of the gland and injected them into animals. There had even been clinical trials in which patients had been treated with pancreatic extracts. These trials were abandoned because the extracts caused toxic effects, and it is quite likely that those toxic effects were really due to an overdose of insulin, methods of biological standardisation being very crude in those days. But it is not enough in therapeutics to have a good idea, even if you try it out on a few patients. The success that came in 1923 was due to the fact that Banting and Best were carried forward by faith that was undaunted by the failures of others, and overcame all difficulties until insulin was a practical proposition. They were greatly helped by the fact that during the period since the time of the earlier experiments a practical method of estimating the blood sugar had been devised. This gave them a quick proof that their extracts were active and a ready means of measuring their activity.

The most remarkable feature of the 1920's taken as a whole was that the U.S.A. suddenly took the lead in the production of new remedies. Only 5 of the remedies in the list have been credited to America in *all* the years before 1920, but during the next 10 years the Americans introduced 8 more of these remedies. Three of these were the result of work in laboratories on bacteriology, physiology and biochemistry. The use of liver in the treatment of pernicious anæmia was discovered by direct clinical trial. This was inspired by theoretical work on anæmia, but it was really an accident that this inspiration led to the right result. Whipple had shown that liver was effective in the treatment of microcytic anæmia in rats. Minot[33] was inspired by the knowledge of this fact to try giving liver to a patient with macrocytic pernicious anæmia, and it worked. The effect on rats was due to copper and the effect on pernicious anæmia was due to a complex organic compound called cyanocobalamin. Liver was tried because it contained copper, and it was a very fortunate coincidence that it happened also to contain cyanocobalamin.

During this period the Americans also produced a respectable number of synthetic remedies though not so many as the Germans, who still held the lead in this field. About half the synthetic drugs in my list for the 1920's are examples of the results of research in chemotherapy. They were discovered by infecting animals with diseases and then comparing the therapeutic effect of large numbers of chemicals. The introduction of carbon tetrachloride was the result of experiments on dogs infected with worms[34]. The introduction of suramin was the result of experiments on mice infected with trypanosomes. The introduction of pamaquin was the result of experiments on canaries infected with malaria[35]. When the Germans could not get quinine in the Kaiser's war they started looking for a substitute. Methylene blue was the only synthetic drug that was known to be effective at that time. They set out to improve on methylene

blue. They attached a side chain to it and by a prolonged series of trials and errors they gradually improved their side chain, testing dozens of drugs in the process. When they had found the perfect side chain, they tried changing the original nucleus to which the side chain was attached, so that when they had finished there was left no vestige of the original methylene blue from which they had started. Some years later they made an even better antimalarial (called atebrin or mepacrine), by attaching the same side chain to another nucleus.

In recent years many thousands of substances have been tested for antimalarial activity using infected chickens and ducklings, and many active compounds have been discovered. The discovery of proguanil was based on ingenious chemical arguments about the shapes of molecules.[36]

During the 1930's Germany lost the lead in therapeutics, although her output was still considerable. It was she who first discovered the wonderful properties of the sulphonamides and she has got all the credit for this achievement, but it is doubtful whether this is just. The activity of sulphanilamide itself was discovered in France, and the first convincing clinical trials and the first derivative more active than sulphanilamide were discovered in Britain and many of the later developments occurred in the U.S.A. In any case, even if Germany is to get all the credit for the sulphonamides her achievement in these 10 years did not obviously exceed either that of the British, or that of the Americans. The combined output of the English-speaking countries was now clearly greater than that of the German-speaking countries.

The discovery of the chemotherapeutic activity of diamidine compounds, such as propamidine, provides an interesting example of the curious ways that new discoveries are sometimes made. Many workers had studied the survival of trypanosomes outside the body. It was found that they used up oxygen rapidly and burned glucose rapidly, and if they were deprived of glucose they became less active and underwent various other changes. It was clear that any drug which deprived the trypansomes of glucose or which prevented them using glucose, would be bad for them. In 1938 two Hungarian scientists Jansco and Jansco[37] came to the conclusion that the drug suramin did actually act in this way and decided to try whether other drugs would do so too. Synthalin causes a fall of blood sugar by poisoning the liver and might be expected to deprive the trypanosomes of their main food. This led them to try the effect of synthalin on mice infected with trypanosomes. The experiments were successful and Jancso and Jancso claimed that this was the first time that it had been possible to discover a compound with chemotherapeutic activity by theoretical reasoning instead of by pure accident. This, they said, was impressive evidence of the importance of the investigation of the mode of action of drugs.

Professor Warrington Yorke[38] of Liverpool was, however, sceptical. It seemed to him unlikely that the hypoglycæmia would kill the trypanosomes before it killed the mouse and he decided to re-examine the phenomenon. He soon found that synthalin killed trypanosomes *in vitro* in concentrations as low as 1 in 200 millions, and of course synthalin does not

cause hypoglycæmia *in vitro*, so that the hypoglycæmia was not the cause of the effect. This conclusion was confirmed by experiments in which insulin caused hypoglycæmia without harming trypanosomes. It is still possible that synthalin acts by interfering with the glucose metabolism of the trypanosomes, but there is now no evidence that this is so. These experiments showed that the drug acted directly on trypanosomes in very low concentrations, and King and Ewins then synthesised a number of similar compounds, several of which proved very effective on trypanosomes, and other microbes.

In spite of the war there was no falling off in the rate of discovery of new remedies between 1940 and 1950. The war itself was in fact a potent stimulus to certain kinds of research and quite a number of new remedies came more or less directly from the work undertaken in connection with chemical warfare. The substance which is known as mustine or chlormethine ($CH_3.N(CH_2CH_2Cl)_2$) was first studied because it acts like mustard gas and it was thought that it might be used in chemical warfare. Its toxic effects were studied in the hope of finding an antidote and it was found that it caused the leucocytes to disappear from the blood. After the war it was used to produce just this effect in leukæmia when there are too many leucocytes in the blood. Drugs of this group were also found to cause mutations by acting on the germ cells in the gonads so that the next generation was abnormal. These were the first drugs known to produce such an effect and they were christened mutagens[39]. Their interest is, of course, academic; doctors don't ever want to produce abnormalities in the next generation. The substance dibenamine also contains a chlorethylamine group and was discovered by investigators who had been working on chemical warfare agents. Its place in therapeutics is not yet established but it is interesting because it causes paralysis of the sympathetic system which lasts longer than that due to any drugs that were known before.

The substance dimercaprol was discovered in the search for an antidote to the arsenical vesicant known as lewisite[40]. It was known that substances containing SH groups combined with arsenic but the combination was more easily reversible than the combination between arsenic and the tissues. After much study it was concluded that arsenic must combine with two neighbouring SH groups in the tissues and it was found that antidotes with two neighbouring SH groups were able to compete on more equal terms with the tissues. The substance dimercaprol was thus found to be a potent antidote for arsenic and for various other toxic elements such as mercury, cadmium, zinc and gold. One reason why it is not more used than it is, is that arsenic poisoning has become rare owing to the use of antibiotics instead or organic arsenicals in the treatment of syphilis.

The anticholinesterases[14] have perhaps aroused more interest than other drugs which have been studied in connection with chemical warfare. These include some of the most poisonous substances known; they have been much used to kill vermin. Men have been poisoned accidentally in peace time and might be poisoned intentionally in war time. More is known about the biochemical explanation of their action than of that of any other class of drug and there is still clearly much to discover. These

drugs are a striking example of the fact that new pharmacological ideas may stimulate other branches of science.

These examples suffice to show that the researches which were undertaken in wartime in connection with chemical warfare have borne various kinds of fruit. Let me now turn to a group of discoveries which have been based on investigations of the ways in which drugs may antagonise one another. One of the earliest examples to be studied was the antagonism between carbon monoxide and oxygen which compete with one another for hæmoglobin. Carbon monoxide forms a much more stable combination than oxygen and a small amount of carbon monoxide can prevent large amounts of oxygen from combining with the hæmoglobin in the blood so that the animal dies. A similar state of affairs was studied by biochemists in many experiments where two substrates were competing for the same enzyme. The importance of this idea of competition was also emphasised by various pharmacological studies of antagonism in the early part of this century[41]. To take one example, Pohl[42] discovered that the insertion of an allyl group instead of a methyl group in codeine produced an antagonist for morphine and believed that this was because the new compound combined with the same groups in the tissue as the morphine but did not produce the same effect. In 1931 Stedman[43] used this theory to explain the action of eserine on cholinesterase. Chemical groups in this enzyme (which are known as receptors) normally combine with acetylcholine and hydrolyse it rapidly. Eserine is an ester like acetylcholine and it may combine with the same receptors so that the acetylcholine is excluded from the receptors and preserved from hydrolysis. It thus became apparent that competition is liable to occur between any two drugs which are closely related to one another and this fact was used for the discovery of new antagonists. It led to the discovery of drugs which antagonise adrenaline and drugs which antagonise histamine. These antihistamines were discovered in Paris during the exciting years between 1937 and 1944 and they were soon found to have many uses, so that they are now almost as popular as aspirin.

In 1940 this theory of competitive inhibition was used to explain the action of sulphonamides. It was found that their action could be inhibited by very small amounts of *p*-aminobenzoic acid and it was suggested by Woods and Fildes that this acid was a growth factor for the organisms the utilisation of which was inhibited by the sulpha drugs. This theory is now generally accepted; *p*-aminobenzoic acid is normally used by the microbes to make folic acid and many of the chemical details of how this occurs and how the sulpha drugs interfere with it are known.

This work with the sulpha drugs did much to popularise the theory of competitive inhibition and led to the discovery of various antivitamins. For example, aminopterin has the same chemical structure as folic acid except that one OH group is replaced by NH_2. It competes with folic acid and prevents the formation of new cells in the body. It has not been found effective in the treatment of cancer, but it is a very powerful and interesting poison and has been used in the treatment of leukæmia because it inhibits the formation of new leucocytes.

The substance dicoumarol was isolated in 1939 as the active substance in a disease of cattle caused by the eating of spoiled clover hay. It interferes with the clotting of the blood. Its resemblance in chemical structure to vitamin K immediately suggested that these two substances were competitive antagonists and this is still thought to be the true explanation of their action[44].

In more recent times substances allied chemically to thyroxine have been found to be antagonists of thyroxine[45].

From the practical point of view the most important recent discoveries have been in the field of chemotherapy. The great potency of diaminodiphenylsulphone (dapsone, B.P.C.) was first discovered by Buttle[46] although the application of its derivatives to tuberculosis was an American discovery. A complex of dapsone was the first drug to be effective in tuberculosis but was quickly replaced by better drugs. However, it forms the essential part of the molecule of solapsone B.P.C., probably the first sulphone to be used to treat leprosy[53]. This drug has completely transformed the position of lepers, who can now be rescued from a life of misery as outcasts, and restored to their families. They say the only difficulty in this programme depends on the fact that it all seems too good to be true and that the lepers' relations can only with difficulty be persuaded that it is safe to welcome the lepers home again.

It is unnecessary to say much about antibiotics. Their properties had been widely studied for many years before the advent of penicillin. In 1929 Fleming followed up a fortunate accident and showed that a mould formed a substance which inhibited bacteria and that this substance was not toxic. In 1940 Florey and Chain and their colleagues made the exciting discovery that this substance had a chemotherapeutic action when injected into infected mice. It was really this observation which showed that it was worth spending much time and money on penicillin and it was the success of penicillin which created a new industry devoted to antibiotics. Active substances have been found in bacteria, and in actinomycetes and other fungi. Many of these organisms were obtained from soil, but penicillin was found in a bacteriological laboratory and the streptomycin-producing organism was found in a chicken's throat. In recent years new antibiotics have appeared in rapid succession and there are now few if any visible microbes simpler than spirochætes which cannot be inhibited by antibiotics. This is a great practical achievement which we owe very largely to the Americans. It can scarcely be said that each new substance is a fundamentally new discovery, but a large proportion of the credit for the revolution in therapy which antibiotics have caused must go to those who were responsible for the practical developments.

Dramatic advances have been made in recent years in the chemotherapy of tuberculosis[47]. Derivatives of dapsone gave promising results in animals but were disappointing when tested on man. The antibiotic streptomycin gave dramatically good results in animals and in human tubercular meningitis and elaborate clinical trials were arranged to test its value in pulmonary tuberculosis. The methods which were devised in connection with these trials have had a very important effect since they

have made it possible for the first time to assess new treatments for tuberculosis in a few months, and various new drugs have been assessed in this way. *p*-Aminosalicylic acid was discovered as the result of fundamental work on the metabolism of the tubercle bacillus. Thiosemicarbazones were discovered as the result of a systematic search based on the fact that sulphathiodiazoles have some curative effect on tuberculous animals[47]. Isoniazid was discovered in much the same way, but the most important fact which has been established by these trials is that when two remedies are used together the organisms are often less liable to develop resistance to either of them. This discovery may revolutionise the treatment not only of tuberculosis, but also of other diseases in which the development of resistant strains is a bar to progress. We have even been told lately that tumours may become resistant to drugs. It is possible that the secret of the cure of cancer may lie in the combination of two or more drugs in this way.

There have, of course, been many other important advances in chemotherapy during recent years. Thousands of new drugs have been tried in the treatment of malaria and some of the new remedies for this very important disease are better than the old remedies. Synthetic drugs have been found to relieve those afflicted with the distressing tropical and subtropical diseases due to bilharzia[48] and filaria[49]. All these things are advances in chemotherapy and they make an impressive list.

It is uncertain whether work on repellants is chemotherapy or not, but the methods of investigation are similar to those used in the study of chemotherapy[50]. In wartime it became especially important to prevent insects from biting men and women, since their bites were not only unpleasant, but liable to transmit dangerous diseases. It was known that if oil of citronella was applied to the skin insects were repelled for a while, but this effect did not last long enough. Systematic researches were therefore undertaken in the Orlando Institute in America in which human arms were smeared with hundreds of compounds and then exposed to healthy and hungry mosquitoes. The time to the first bite was measured and so it was found that dimethylphthalate had a prolonged effect and this substance is now widely used to repel mosquitoes and midges and allied creatures.

The most interesting discoveries are the unexpected ones, and in spite of the fact that research is much more organised to-day than it was once, unexpected discoveries are still made. In 1948 Hald, Jacobsen and Larsen[51] were interested in the substance tetraethyl thiuram disulphide because it combines with copper and they hoped to kill intestinal parasites by depriving them of copper. Experiments on animals had given promising results and the substance did not appear to be very toxic, but they found that when the substance, which is now known as disulfiram or antabuse, had been taken, alcohol always caused flushing, headaches, nausea and vomiting so that those who were normally too fond of alcohol lost their desire for it. Disulfiram now plays a useful part in the treatment of chronic alcoholism but Hald and Jacobsen were not content with this and continued their experiments until they found out how it worked. They noticed a smell of acetaldehyde and this led them to the biochemical

explanation of their discovery. Ethyl alcohol is normally oxidised in the body first to acetaldehyde and then to acetic acid. Disulfiram inhibits the second reaction and so causes the accumulation of acetaldehyde in the body and it is this which causes the symptoms. The moral of this tale is that even such things as unexplained headaches may be turned into important discoveries when someone has the energy and skill to seize the opportunity.

Another example of an unexpected discovery is the work of Hofmann and Stoll on lysergic acid diethylamide[52]. Hofmann was working on the chemistry of ergot derivatives in Basel and one day he felt very queer indeed. The whole world looked unusual and he had difficulty in getting home. Next day he felt better and wondered to himself whether perhaps he had been poisoned by the lysergic acid diethylamide which he had been making. In order to test the theory he took 0.25 mg. by the mouth and the effects were worse than ever. This is now recognised as one of the most active known drugs. A dose of 0.03 to 0.05 mg. by the mouth causes a condition resembling schizophrenia but lasting only for a few hours. The victim feels as if his own body does not belong to him and is intensely aware of the world around him which looks like a picture by a surrealist. Anyone who can get this stuff can now tell what it feels like to be mad. In the end this discovery may throw light on the action of the brain. In the meantime it presents a fascinating problem but has no obvious practical applications.

What are the general impressions produced by this rapid review of the origins of some of the drugs of today?

The most important fact is that, in the words of Starling: "Every discovery however important and apparently epoch-making, is but the natural and inevitable outcome of a vast mass of work, involving many failures, by a host of different observers." It is true that many discoveries have been accidents, but these accidents would not have occurred to anyone who was not engaged on a systematic search for new knowledge, and without all the technique and apparatus of modern science they would usually have passed unheeded by the world at large. Jansco and Jansco would never have discovered the effects of synthalin on trypanosomes if they had not been engaged on systematic pharmacological experiments. They had a lucky accident, but it was only because they were expert in the technique of chemotherapy that they were able to prove a new fact and give it to the world. This fact might, however, quite easily have been lost in the limbo of forgotten achievements buried in the back numbers of scientific journals, if Yorke and King and Ewins had not confirmed it and developed it until they had discovered a whole group of new remedies.

It is of course true that chance has played an important part in the discovery of new synthetic remedies. It seems likely to play a less important part in the future. New types of drug do seem to have been discovered recently in the light of pure reason, but we must be warned by the example of Jansco and Jansco who gave too much credit to the intellect in discussing the origins of their own discovery. It will probably always be more important to try a thing out, than to argue about it.

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