Table I.—Grain Size Distribution of Particles as Percentage by Weight Finer than Size in Six Samples of Bismuth Subsalicylate, U. S. P. XI

T (Min.)	H (Cm.)	Grain Size (Microns)	Percentage by Weight Finer than Size Mfg. A	Mfg. B	Mfg. C	Mfg. D	Mfg. E (Reg.)	Mfg. E (Spec.)
5	19.7	18.68	78.6	87.8	87.4	83.2	86.4	98.6
15	19.4	10.70	69.4	87.4	84.4	82.6	79.8	98.0
30	19.0	7.48	55.4	77.2	74.8	76.8	12.6	96.0
60	18.7	5.24	54.0	50.6	62.8	63.4	7.0	95.6
120	18.4	3.68	27.6	30.4	52.2	39.2	3.8	92.8
240	18.0	2.57	20.2	18.6	39.4	17.4	3.0	90.4
360	17.7	2.08	15.6	14.6	31.8	11.2	2.6	90.0
1440	17.4	1.02	6.4	4.0	18.2	2.2	1.4	76.2

Table II.—Grain Size of Particles as Percentages by Weight in Distribution Intervals in Six Samples of Bismuth Subsalicylate, U. S. P. XI

Mfg.	< –1.02 μ	1.02–2.57 μ	2.57–7.48 μ	7.48–18.68 μ	>18.68
A	6.4	13.8	35.2	23.2	21.4
B	4.0	14.6	58.6	10.6	12.2
C	18.2	21.2	35.4	12.6	12.6
D	2.2	15.2	59.4	6.4	16.8
E (Reg.)	1.4	1.6	9.6	73.8	13.6
E (Spec.)	76.2	14.2	5.6	2.6	1.4

sion of the salt is essential, we have determined the grain size distribution in six commercial samples of this drug.

EXPERIMENTAL

The test was conducted by the method described by the authors in a previous communication to this JOURNAL (3). The grain size was calculated from Stoke's law according to the falling velocities of the particles (h/t). When the test is conducted at 25° C. on material with a specific gravity of 3.0 and distilled water used as the suspending medium,

$$r \text{ is equal to } 5.84\sqrt{H/T} \quad (1)$$

with r, the radius of a spherical particle, in microns; H in cm. and T in minutes. Applying Stoke's law to cubes, the width of a cube is equal to 1.612 r. Thus, the grain size of the particles, calculated as cubes is

$$\text{Grain size is equal to } 9.414\sqrt{H/T} \quad (2)$$

The results are tabulated in Tables I and II.

SUMMARY

1. The grain size distribution in six samples of Bismuth Subsalicylate, U. S. P. XI has been determined.

2. In five of the six samples tested, 80 per cent of the particles have a grain size less than 20 microns. In one sample (labeled "special" by the manufacturer), 90 per cent of the particles have a grain size less than 3 microns.

CONCLUSIONS

The Pharmacopœia might properly describe Bismuth Subsalicylate as an amorphous or microcrystalline powder in which not less than 80 per cent of the particles have a grain size smaller than 20 microns.

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The Vitamin B Complex*

(A Review)

By Douglas Frost†

INTRODUCTION

Few subjects could offer more lively interest or greater intricacy of thought than that of the vitamin B-complex. What it is, where it is found, how it functions, how its presence can be detected and quantitatively assessed, and how it can best be used, are questions of fundamental importance in biology and medicine. Indeed, they are tantamount to our understanding of many of the innermost secrets of cellular life.

Although the idea of the vitamin B complex was born in the minds of a few farseeing men several decades ago, it remained quite vague and intangible in the popular mind until only recently. Now we are on very firm ground in discussing the B com-

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plex, and particularly those five crystalline, synthetic B-complex vitamins which intensive research has made available to us in a few short years. Thiamin (vitamin B_1), riboflavin (part of vitamin B_2), nicotinic acid (part of vitamin B_2), pyridoxine (vitamin B_6—identical with B_5) and pantothenic acid (identical with B_3) are all well-characterized chemical compounds and are now being synthesized on a large scale. There is no more mystery about those compounds from an organic chemist's point of view than there is about aniline, phenolphthalein or the amino acids.

BIOLOGICAL SIGNIFICANCE

From the biochemist's point of view, certain facts about the above five compounds appear to stand out and to make understandable their role in life processes. These facts serve to establish the importance of the vitamin B complex generally and to show how logical its place in biological science has become.

1. All five B-complex vitamins occur in relatively high amount in actively metabolizing tissue, such as liver and kidney. They also occur in high amount in yeast and bacteria, and also in seeds and sprouts of all plants.

2. Each of the five is known to function as the active grouping of an enzyme system intimately concerned with intermediary metabolism, and is known to affect the rate of metabolism adversely in its deficiency. Probably each one is essential to the metabolic integrity of all living things.

3. Although differing widely in chemical nature, each of these compounds, as it occurs naturally, is water-soluble and is capable of forming soluble protein complexes.

4. All of them have been shown to stimulate the growth of rats, chickens and dogs when given in extremely small amounts. All of them have been shown to stimulate growth in certain species of plants and microorganisms. Thus they can be regarded as the organic catalysts of metabolism, which may or may not be required in the nutrition, depending on the species in question.

HISTORY

The story of the vitamin B complex has unfolded rapidly in the last six years. Each year has seen the isolation, characterization or synthesis of one of the above-mentioned generally recognized B-complex vitamins. To recount the immense number of experiments and observations which led to the eventual isolation, characterization and synthesis of any one of them would require several volumes. A number of books (1, 2, 3) have already appeared to tell the story of vitamin B_1. Reviews on riboflavin (4, 5), nicotinic acid (5), vitamin B_6 and pantothenic acid have also appeared. In this brief review I cannot begin to do justice to these stories. Suffice it to say that the isolation of each of the five compounds as biologically important substances followed somewhat the same pattern. Thus, the heat-stable factor in yeast, liver, eggs and milk, which has so much to do with the growth-promoting value of these foods, turned out to be riboflavin, the same beautiful yellow pigment of milk serum, the occurrence of which was reported in 1784 (6). Simultaneously with the announcement of its isolation as a growth factor for rats in 1932 (7) came the news that this same yellow pigment is the prosthetic group of an enzyme which occurs in yeast and has a great deal to do with the mechanism of fermentation (8). In rapid order, riboflavin was isolated from milk, eggs, liver, kidney, urine and barley. Because it was a new compound, unknown to organic chemists, it had to be characterized. When the nature of the compound was determined, the generic name "flavin" was applied to it and to similar type compounds which might be subsequently isolated or synthesized in the laboratory. As it turned out, *d*-riboflavin is the only naturally occurring flavin, although a great number of other flavins have been made. As might be expected, Nature made no mistake in making riboflavin as it did, for, of all the flavins, riboflavin is most active in all species, whether in plants or in animals.

The substance in liver extracts which had most to do with the cure of black-tongue in dogs and which, according to Goldberger, might be expected to cure the analogous disease, pellagra, in humans, turned out to be nicotinic acid (9). Nicotinic acid had been made from nicotine in 1867 (10) and had been isolated by Funk in 1912 (11) in his search for vitamin B_1. In fact, nicotinic acid had followed Funk's fractions so closely that he had patented the procedure for isolation of crystals which were undoubtedly nicotinic acid, but which carried sufficient vitamin B_1 as an impurity to be a relatively rich source of that vitamin. The fundamental discovery of Warburg (12) that nicotinamide is the functional grouping of an important respiration enzyme found in blood cells provided the clue (13) which led directly to recognition (9) of the nutritional importance of nicotinic acid and its derivatives.

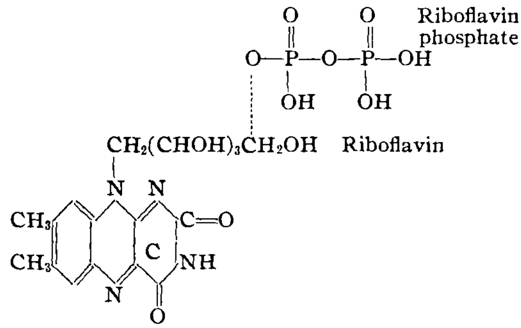
Vitamin B_6 was isolated from rice bran concentrates (14) as the curative factor for a typical dermatitis in rats called acrodynia. When the pure compound became available it was found to do many surprising things. It promptly cured a certain type of microcytic anemia in dogs (15) and pigs. It promoted the growth of chicks (16) and microorganisms (17) and it has been reported to relieve muscle dystrophy in humans (18).

Pantothenic acid (19) was first recognized about 20 years ago as a growth factor for yeast. Its final characterization (20) was made possible as a specific growth factor for yeast and for lactic acid-producing bacteria and as the chick antidermatitis vitamin. Although synthesis of pantothenic acid was announced only eight months ago, it is already known to be required by chicks (21), rats (22) and dogs (23), and there is some evidence that it plays a role in human nutrition (24) as well.

Chemistry and Stability of the B-Complex Factors.—Thiamin hydrochloride has the structure:

This is the form in which synthetic thiamin is dispensed generally. About 80–90% of naturally occurring thiamin is found as the pyrophosphoric acid ester, cocarboxylase. Unfortunately, thiamin is not as stable as cocarboxylase under certain conditions and requires special handling. Both thiamin and cocarboxylase are destroyed by heat and alkali. Thiamin is destroyed also by even mild reducing agents. Stabilization of thiamin can be accomplished in many pharmaceutical preparations, but the job is not so easy as it may seem.

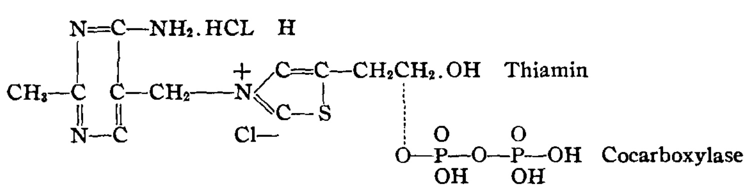
The first heat-stable B-complex vitamin to be recognized as such was riboflavin.



In the free form it is only sparingly soluble in water (0.025%). In its natural form it exists as the pyrophosphate and in combination with adenylic acid and various proteins (*d*-amino acid oxidase, diaphorase, flavin-adenine-dinucleotide).

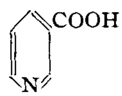
Riboflavin is stable to heat and to strong acids. It is destroyed by alkali and by light. Destruction by light is extremely rapid at alkaline p_H and is appreciable at acid p_H. Both riboflavin and thiamin are quite stable to atmospheric oxygen and to hydrogen peroxide.

Riboflavin is reversibly oxidized to colorless leucoflavin by the proper reducing agents, such as bisulfite, and is rapidly oxidized back to the original yellow compound by merely shaking in presence of oxygen.

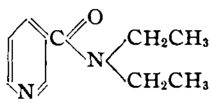


It is this property of easy reversible reduction and oxidation which explains the role of riboflavin in biological oxidations.

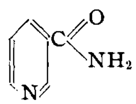
The formula of nicotinic acid is quite simple.



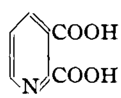
Many analogues are active, including:



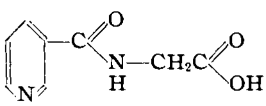
Nikethamide (Coramine)
(Diethyl nicotinamide)



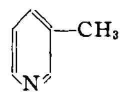
Nicotinamide



Quinolinic acid

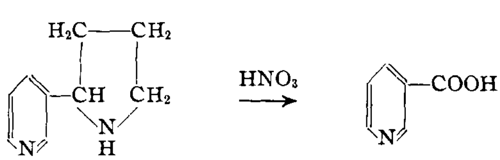


Nicotinuric acid
(Nicotinyl glycine)



B-Picoline

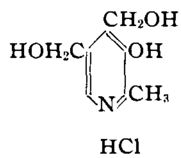
In fact, any compound which yields β-carboxy or β-amido pyridine when taken into the body might be expected to have some anti-pellagric action. Even nicotine, which is the chief source of the manufacture of nicotinic acid chemically, may yield traces of nicotinic acid in the body. It is odd that nicotine, a compound second to hydrocyanic acid in the swiftness with which it will cause death of animals, is so closely related to compounds essential to all life. It also provokes tribute to the long-continued research, much of it into fields of pure knowledge, which makes such a useful transition possible.



Nicotine → Nicotinic acid

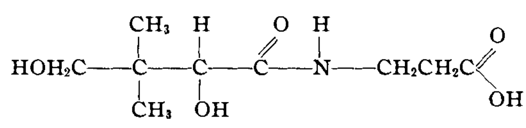
From a chemical and pharmaceutical standpoint, nicotinic acid presents the least difficulties of any of the B-complex vitamins. Nicotinic acid is one of the most stable compounds known to organic chemistry, and nicotinamide is quite stable to ordinary pharmaceutical handling. From a pharmacologic standpoint, nicotinamide is the compound of choice because it is less apt to give the unpleasant secondary flushing and tingling sensations experienced with even small doses of nicotinic acid. Also nicotinamide is much more water-soluble than nicotinic acid, which is usually dispensed as the soluble sodium or ethanolamine salts.

Pyridoxine, formerly known as vitamin B_6 adermin, factor *I*, and factor *Y*, is also a substituted pyridine.



It is quite water-soluble and quite stable to heat, oxidation and acid. It is less stable to alkali and is quite rapidly destroyed by alkaline oxidation. Pyridoxine is amphoteric but, unlike nicotinic acid, it is a stronger base than an acid and is quite generally dispensed in the form of its hydrochloric acid salt. Pyridoxine contains a phenolic hydroxyl grouping and undergoes many type reactions of the phenols, some of which are useful analytically and will be discussed later.

The most recently synthesized member of the vitamin-B complex is pantothenic acid:



It is formed by the interaction of α,γ-dihydroxy-β,β-dimethyl butyric acid with β-alanine. It is destroyed by dry heating or by acid or alkaline hydrolysis and is handled safely only as its neutral salts. Pantothenic acid is dispensed pharmaceutically as the nicely powdered calcium salt. A concentrated water solution of this has a p_H about 8. The p_H of greatest stability is thought to be between 5 and 6. Pantothenic acid is stable to oxidation in air and is stable to ordinary light.

Table I

	Heat	Acid	Alkali	Oxidation	Light
Thiamin	+	++	−	−	++
Riboflavin	++	+++	−	+++	−
Nicotinic acid	+++	+++	+++	+++	+++
Pyridoxine	++	++	−	−	++
Pa A	−	−	−	++	++

+++ = stable, ++ = very slowly destroyed, + = slowly destroyed, − = rapidly destroyed.

Table I indicates the relative stability of the five synthetic B-complex vitamins in aqueous solution under various conditions. Although such a table is of general value, it should be realized that many conditions other than those indicated may contribute to the instability of these compounds and much experimentation must be done before positive assurance of their stability in any preparation can be had. Also the time of reaction is important and a preparation which may appear stable for a week may show a significant decline in potency in a month. Temperature, p_H, oxidation-reduction potential and the nature of the solvent are factors in the stability of all, excepting only nicotinic acid, which is remarkably stable under most conditions.

ANALYSIS

There are rapid chemical or microbiological methods of analysis available now for each of the five mentioned compounds. In some cases these methods are actual improvements from the standpoint of accuracy over the animal assay methods.

Wide use is being made of the thiochrome method of analysis for thiamin (25). In this method cocarboxylase can be converted to free thiamin by hydrolysis in acid. The total thiamin is then oxidized to the blue fluorescent thiochrome by ferricyanide and the thiochrome quantitatively measured in a photoelectric fluorometer. The method is both rapid and accurate and can replace the animal assay in routine testing of many materials.

Vitamin B_6 reacts with such well-known phenol reagents as diazotized sulfanilic acid, the Folin-Denis reagent, and 2,6-dichloroquinone chlorimide. The last reagent produces a blue color soluble in butyl alcohol, which can be measured quantitatively in the photoelectric colorimeter (26). Animal assay methods may be relied upon to check the accuracy of this method. Both cure of acrodynia and growth increment are useful as an index to B_6 potency of materials.

The reaction of nicotinamide and nicotinic acid with cyanogen bromide and an aromatic amine has been extensively studied for its analytical value. The method has been adapted to photoelectric colorimetry (27) and is quite dependable for routine assay of many materials. Cure of blacktongue in dogs is used wherever necessary, but the method is long, cumbersome and of questionable accuracy.

Microbiological assay methods have great promise for routine testing. The assay of riboflavin and pantothenic acid may be accomplished by use of the same organism, *lactobacillus casei*, with only slight variation in technique (28, 29). In this method media are prepared free of either riboflavin or pantothenic acid, whichever is to be analyzed for. The growth and amount of lactic acid produced by *lactobacillus casei* on these media under the proper conditions are an exact measure of the amount of flavin or pantothenic acid added. The method is sensitive to 0.05 microgram of either compound and is accurate to ±10%.

PHARMACOLOGY

All five compounds have had adequate pharmacological testing with animals (30, 31, 32, 33, 34). The margin of safety between the effective dose and the lethal dose was extremely large in all cases. Massive doses (50–100 times the estimated requirement) have been given to humans with no untoward effect.

HUMAN REQUIREMENT

The daily adult human need for these factors is on the order of:

Thiamin	2–3 mg.
Riboflavin	3–4 mg.
Nicotinic acid	15–25 mg.
Pyridoxine	2–3 mg. (estimated)
Pantothenic acid	15–20 mg. (estimated)

The need for pyridoxine and pantothenic acid in human nutrition has only been tentatively established, but there is little doubt that such a need exists. The requirements of growing children for all of these factors are probably as great as those of adults, and the requirements of pregnancy and lactation are probably double those of normal. Much research must be done to determine the optimal intake of these factors under all conditions of health and disease. Reviews on this phase of research have recently appeared (35, 36, 37, 38, 39).

NEWER MEMBERS OF THE VITAMIN B COMPLEX

As far as the new members of the B complex go, we can definitely say that the end is not yet. Although rats can be raised to the adult stage on highly synthetic diets with only the five synthetic B-complex vitamins plus choline, there is good evidence that other factors are needed for optimal health. Pyridoxine and pantothenic acid are undoubtedly the two most important growth-promoting substances of the so-called "filtrate factors" fraction obtained from liver, yeast, rice bran and other good B-complex sources. The additional growth-promoting property of the ether-insoluble filtrate fraction from liver has been ascribed to Factor *W* (22, 23).

Present knowledge relates choline to the B complex; however, it appears to be required in higher amount than the other factors and is synthesized to large extent *in vivo* (40, 41).

Inositol and biotin, long known to be required for growth of yeast as members of the "bios" complex, are now recognized as members of the B complex. Biotin has proved to be identical with vitamin H, the anti-egg white injury factor for rats (42), and is essential to normal pelage in chicks (43) and rats (44). Inositol is required for growth and maintenance of normal fur coats in mice (45) and rats (46).

The disclosure that deficiency of the filtrate fraction of the vitamin B complex causes a predilection toward graying of the fur in rats, foxes, dogs and guinea pigs (47) raised the burning question as to what factors are specifically involved. Pantothenic acid appears now to be most intimately concerned with pigmentation in rats (48, 49), but other factors appear to be involved (50, 51, 52). Recently *p*-amino benzoic acid, which had previously been named as a growth factor for microörganisms, was reported (53) to be a growth factor for chicks and a chromotrichia factor for rats. These findings require confirmation before the importance of *p*-amino benzoic nutritionally can be established. Almost nothing is yet known of the relation of diet to graying in humans.

"Anticanitic," a term which means "opposed to graying of hair," has been proposed (54) as offering some advantages over "anti-achromotrichia" for designation of the various "anti-gray hair" factors.

COMPARATIVE NUTRITIONAL REQUIREMENTS OF SPECIES

Generally, it seems that the more complicated the organism, the more complex are its nutritional requirements, and it seems probable that the requirements of man will eventually be found to comprehend the requirements of all species. Also it seems that the more parasitic an organism is, the more uncompromising it is in its demands from its environment. Thus most pathogenic bacteria must obtain many of the B-complex factors from the tissues or blood of their host, while others (the autotrophs) can live on air and a bit of carbon, sulfur or even iron.

Undoubtedly bacterial symbiosis plays a large part in the nutrition of many forms of animal life. Cattle and sheep are good examples of one extreme in nature's plan of synergistic action between living things. Here all or a large share of the animal's B-complex requirements are supplied by synthesis by bacteria in the animal's paunch. The nutritional requirements of ruminants are greatly simplified by this mechanism. The large majority of animals, on the other hand, require most B-complex factors preformed in the diet. Rats, dogs and pigs are the most studied members of this group, which includes the human. In the case of the rat, certain diets have been demonstrated to favor bacterial synthesis of B-complex vitamins more than others, and difficulty in producing acute specific deficiencies is often experienced because of the uncontrolled generation of B-complex factors in the animal's tract. The chick is probably least helped by bacterial action, and this may be evidenced by its very complex needs for nutritional factors. Biotin, choline, inositol, *p*-amino benzoic acid, glycine, chondroitin, factor *U*, and factor B_c are some of the compounds and hypothetical factors included among the nutritive requirements of the chick. The nutritive requirements of man have not been completely delineated as yet and the job will be a difficult one; however, workers in this ripe field can draw on a wealth of inference derived from work with many animal species.

An increased or decreased ability to synthesize certain B-complex vitamins can be demonstrated in certain bacteria by culturing them through a great many generations in absence or presence of the compounds in question. This sort of biogenetical adaptation to environment can account for some of the variations in the requirements of higher species. Meat is a good source of nicotinic acid, thus naturally carnivorous animals, *i. e.*, all members of the canine and feline families, may be expected to require nicotinic acid preformed in their diets. It is probably safe to predict, then, that lions, jackals and even sharks could be reduced to a pitiful state of inefficiency, just as are dogs, cats and man, by cutting off their supply or utilization of the single factor, nicotinic acid.

Certain processes, wherever they occur in living things, apparently require the intermediation, or catalytic function, of thiamin, riboflavin and nicotinamide. This fundamental action is probably equally true, though less well proved at present, for pyridoxine and pantothenic acid. This select group of fundamental water-soluble metabolic catalysts will probably extend in time to include biotin and one or two other previously mentioned compounds, but the most useful and important ones are already in our hands.

Someone has remarked that "It is the intuition of unity amid diversity which impels science." This well-phrased truth was almost undoubtedly not inspired by early work on the vitamin B complex, but might have been so inspired in recent years when the unity of occurrence, distribution and function of the B complex in nature has become increasingly apparent.

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Book Reviews

The Ring Index, by AUSTIN M. PATTERSON and LEONARD T. CAPELL. 661 pages. 6 x 9. 1940. New York: Reinhold Publ. Corp. $8.00.

This is a catalog of 3978 ring compounds compiled by the author for the purpose of systematizing and classifying the ring systems. Each compound is illustrated with a structural formula, its name and at least one reference to the chemical literature. The systems are classified according to the number of rings. A subclassification shows if the ring is carbocyclic or heterocyclic, fused, bridged or spiro. The volume represents work done over approximately twenty years and it is believed that it will be found to be a valuable addition to every chemical library.—A. G. D.

The Life of Ira Remsen, by FREDERICK H. GETMAN. 172 pages. $6^1/_8$ x $9^1/_4$. 1940. Easton, Pa.: Journal of Chemical Education. $2.50.

This little volume is an interesting sketch of the life of Ira Remsen who lived during the period in which chemistry as a science was building up in this country. Ira Remsen, chemist, professor and college president, was schooled in Germany under Liebig, Volhard, Fittig and Wöhler. He was one of the first in this country to appreciate the value of laboratory instruction in chemistry and during his long sojourn at Johns Hopkins as professor and president, he saw that institution rise to a position of one of the foremost among education institutions in the country. The book is full of inspiration and is worth reading.—A. G. D.

Photodynamic Action and Diseases Caused by Light, by HAROLD FRANCIS BLUM. A. C. S. Monograph 85. 309 pages. 1941. New York: Reinhold Publishing Corp. $6.00.

This volume is a critical study of the rather extensive literature on photodynamic action and its relation to certain diseases of man and animals. It begins with a brief, but clear introduction on the nature of radiation and its biological effects. The succeeding section discusses photodynamic action in which consideration is given to the factors determining photodynamic effectiveness and their bearing on the theory proposed. Part III, which deals with the diseases produced by light in animals, gives an interesting account of hypericism, geeldikkop and fagopyrism. Part IV discusses in detail the diseases produced by light in man, both those caused by abnormal sensitivity to ultraviolet radiation and those caused by sensitization to visible light. The relation of light to skin cancer is also discussed. The book represents a very complete survey of the progress which has been made in the study of photodynamic action and should be of interest to the specialist in this field primarily, also to physicians and pharmacists.—A. G. D.