The principal fraction, namely 245 to 255°, had a sesquiterpene odor; $d_{23}°$ 0.912, $\alpha_{D22.5°}$ −10.61°; $n_{D23°}$ 1.494; hence molecular refraction 65.08. According to density, therefore, it belongs to the dicyclic sesquiterpenes, according to molecular refraction between dicyclic and tricyclic. However, the amount of material was too small to insure anything more than a rough separation by fractionation.

A caryophyllene nitrosite test with 3 cc yielded a blue color, but no crystals. Other tests for sesquiterpenes, also Baeyer's test for pulegone, gave negative results. The fractions tested were so small and the material, after but one fractionation, too impure to afford satisfactory results. It becomes apparent that with the high lactone content it will require a large amount of material to separate the several non-lactone constituents in sufficient purity and quantity for identification.

THE MANUFACTURE OF SYNTHETIC MEDICINAL CHEMICALS IN AMERICA.*

BY ALFRED S. BURDICK, M.D.

Before the Great War, this country cut a small, indeed, an almost contemptible figure in the manufacture of synthetic chemicals of all kinds, and particularly in the production of synthetic medicinals. It is not the province of this paper to discuss the tremendous progress which has been made in the manufacture of dyes, although, as a matter of fact, dye production and the production of medicinals are so closely interwoven as to be almost inseparable for a clear understanding of the subject. Sufficient to say that in spite of the fact that the United States had almost illimitable sources to draw on for raw materials through its coal mines, coke ovens and gas plants, its manufacture of medicinal synthetics prior to 1914 was virtually limited to the salicylates, including salicylic acid and its salts, acetylsalicylic acid and salol. These substances were made in this country entirely by German-owned corporations.

A few other synthetics of closely allied character were being produced in small quantities, the principal ones being saccharin (the invention of an American chemist) and phenolphthalein, the manufacture of both of which was begun, I believe, by the Monsanto Chemical Company prior to 1914. Argyrol, which was also introduced by an American chemist, was being manufactured, but, strictly speaking, this can hardly be called a synthetic. I believe that these are the only medicinals, or near-medicinals, which we produced in any considerable quantity prior to this time.

If we consider this small beginning, and consider also the fact that our chemists were but inadequately trained to undertake the tremendous problem of manufacture of medicinal chemicals in this country, as compared with German chemists, whose work rested upon the secure foundation of many years of great achievement, all Americans have just reason to take pride and satisfaction in the accomplishments of the next few years.

Under the stress of necessity, and responding to the call of the government, a number of American manufacturers undertook the production of the most important synthetic medicinals. The number of those which might really be called indispensable was not as large as most of us may have been led to believe Per-

* Read before Chicago Branch A. Ph. A., January meeting, 1922.

haps there were a dozen all told, and of these all are now being made in the United States. Of course there are many other interesting and valuable synthetic remedies which are made in Germany at the present time and which are not as yet produced here, but for the most part these are remedies of minor importance for one reason or another—perhaps because they are used to replace other remedies of similar action and possibly equal merit, or because they have but a limited field of usefulness.

Of the really important remedies the manufacture of which in America was brought about by the war, probably the most important is arsphenamine (commonly known as salvarsan). Of the other synthetic medicinals made in this country, next in importance and of greater value from a commercial point of view is aspirin or acetylsalicylic acid. Other synthetics now produced in this country, in about the order of their importance commercially, are acetanilid, barbital (formerly known as veronal), barbital sodium and luminal—chemically closely allied—cinchophen (formerly known as atophan) and neocinchophen, procaine (formerly known as novocaine), anesthesin and orthoform, and sulphonol and trionol. All of these were originally German patented products, although the patents on some of them had expired prior to the war.

The problem which immediately presented itself was that of German patents. Our government was anxious that the most essential of these medicinals should be produced, but the American patents of such important things as salvarsan, veronal, luminal, atophan and novocaine were the property of enemy aliens. This difficulty was overcome by the passing of the Trading with the Enemy Act, which authorized the issuance by the Federal Trade Commission of licenses to manufacture these chemicals.

In order that the maker might receive reasonable protection for his investment, these licenses were made to run for the life of the patent, and the interest of the alien owner was protected by requiring the deposit with the Alien Property Custodian of a 5 percent royalty upon sales.

Following the passage of this law, a number of American houses were approached by representatives of the government with the suggestion that they undertake the manufacture of one or more of these products The Abbott Laboratories, which I have the honor to represent, was one of the manufacturing concerns which undertook this problem. We immediately began the necessary research work, and eventually manufactured three of these products under license—at first only for use in the Army and Navy. These three products were those then known as veronal, novocaine and atophan.

The Federal Trade Commission gave no exclusive licenses under the German patents. In every instance two, and in several instances three manufacturers were licensed to produce each product. It was not the policy of the Commission to give an unlimited number of licenses, because it was realized that the manufacturer going into this business was in a sense commandeered to undertake a patriotic duty; that before he could produce them large amounts of money would be expended in research; that it was exceedingly doubtful whether the undertaking would be a profitable one, at least for some of these chemicals; and finally that the close of the war, with uncertainty as to terms of peace, might bring all this effort and expense to naught.

Houses were selected by the government for the manufacture of these chemicals which already had some experience in synthetic work. From 1914 to 1917 The Abbott Laboratories had developed the manufacture of certain synthetic products. Soon after the opening of the Great War it began the manufacture of hydrochinone. The venture was not profitable, but it gave us experience. In 1916, following the renewal of interest in antiseptics brought about by the work of Carrel and Dakin in France, we had undertaken the manufacture of the chloramines, which have been favorably received by the medical profession. We had developed a fine chemical staff, and we thought we knew something about synthetic products. During the next two years we learned a lot, and it cost us a pretty penny; but when the war was over we had the satisfaction of knowing that we could make veronal, novocaine, atophan, chlorazene, dichloramine-T, anesthesin, and some other things, as well as, and of as good quality as any European manufacturing house.

It may interest you to know something about the present status of manufacture of synthetic medicinals by American houses. I will take up the most important and give you in a few words what I can which may be of interest to you.

Arsphenamine.—This is the substance formerly known as salvarsan. It was renamed "arsphenamine" by the United States Federal Trade Commission, upon the recommendation of the American Medical Association and the National Research Council. (I may say in passing that all of these German chemicals were given new names, particularly for the purpose of Americanizing these products to protect the American manufacturers, and for the purpose of fostering their continued production in this country after the war. These names were accepted by the Council on Pharmacy and Chemistry of the A. M. A. and will undoubtedly be made official in the next U. S. P.)

The first licenses for the manufacture of arsphenamine were issued to the Dermatological Research Laboratories of Philadelphia and to H. A. Metz & Co. of New York. The latter was the former American agent for the German manufacturer. The Dermatological Research Laboratories was the first to produce this difficult and important chemical in this country, and for some time before he was able to manufacture it himself supplied Metz with the product which he marketed. Not only did the Dermatological Research Laboratories produce arsphenamine of a quality equal to that manufactured in Germany, but it was able to cut the price to one-half and then considerably less, the result being a saving to American consumers of millions of dollars.

Before the war, at a congressional committee hearing in Washington the statement was made that more than a million doses of German salvarsan were being sold in this country. At the present time the consumption is probably considerably greater. There are said to be ten million cases of syphilis in the United States, so that the demand for this drug is enormous. There are now some five or six licensees, including the Takamine Laboratories, E. R. Squibb & Sons, the Mallinckrodt Chemical Works, and the Diarsenol Co., in addition to those already mentioned. Arsphenamine is being produced of a quality unexcelled in any country in the world. It is a difficult chemical to make, and on account of its toxicity it is important that it should be carefully supervised by a competent authority.

This is taken care of by the U. S. Public Health Service, under conditions which make it practically impossible for a chemical of inferior quality to be offered for sale.

Aspirin.—The patent on this product expired before the Great War, but the trade mark has been the subject of litigation for several years, and the case is still pending. It is manufactured by a number of American houses. The United States is now probably the largest manufacturer as well as the greatest consumer of this product in the world. According to the 1920 Census of Dyes and Coal Tar Chemicals, 1,708,436 pounds of aspirin were produced here in 1919. It is probable that the present output is in the neighborhood of two million pounds a year. This is the equivalent of 2,800,000,000 5-grain tablets, and at retail must bring at least $25,000,000.

Acetanilid.—I mention this drug mainly on account of the large quantity which is being manufactured and used. According to the Dye and Coal Tar Census, 1,255,140 pounds were made in this country in 1919. Doubtless a large share of this goes into proprietary headache powders and tablets.

Barbital (Introduced as Veronal).—Authentic figures concerning the volume produced in this country are not available. Judging from our own experience with the product, and only guessing at the amount produced by other manufacturers, I should say the total American production is more than 10,000 pounds a year. Licenses were issued for its manufacture to Antoine Chiris & Co., the Rector Chemical Company and the Abbott Laboratories. As far as I know, the Rector Chemical Company has never produced it in appreciable quantities.

Upon the sale of the assets of the German house of Bayer to the Sterling Products Company, the barbital patent was acquired by this American firm; manufacture was undertaken by the American house of Bayer, its assignee, and the product is now being sold under license from that corporation by the Winthrop Chemical Company of New York. At the present time there are three manufacturers only—Bayer (Winthrop), Chiris and Abbott.

American-made barbital (veronal) is now selling in this country at about half the price asked by German manufacturers in America before the war. In spite of this, Europeans are clamoring for the admission of their product and have offered it for sale in this country at prices only slightly more than the cost of intermediates and raw materials. Considerable quantities have been smuggled into the United States. If American manufacturers are given adequate protection during the critical period of the next few years they will be able to meet any reasonable competition.

Barbital-Sodium, the action of which is virtually identical with that of barbital, is manufactured by The Abbott Laboratories, but the sales are small as compared with barbital.

Cinchophen.—Licenses for the manufacture of cinchophen were issued by the Federal Trade Commission to a number of houses, but at the present time only three or perhaps four concerns are producing it in the United States. Until very recently The Abbott Laboratories manufactured it under license from the Federal Trade Commission. At present all producers are manufacturing under license from The Chemical Foundation. Besides our own firm, it is manufactured by the Calco Chemical Company, and by Schering & Glatz, the last firm controlling the trade-marked name citophen.

Cinchophen, and to a less degree neocinchophen (also made by the Calco Company under trade name Tolysin) has been one of the surprises in chemical manufacture. Before the war atophan was used for the treatment of gout, and for this purpose only. During the last two years particularly, the demand for it has greatly increased—probably because it has been shown to be efficient in the treatment of acute rheumatism and rheumatic conditions generally. Papers by such men as Hanzlik, Chace, Meyer and others have shown it to be less irritant to the stomach and less harmful to the kidneys than the salicylates, while it is equally efficient, if not more efficient, for the relief of pain and as an eliminant. I have reason to believe that many physicians are prescribing it instead of aspirin. Probably 30,000 pounds of cinchophen are being made annually in this country. It is being produced in this country at least as cheaply as in England. German costs of production I am not familiar with. Cinchophen will undoubtedly be the official name of this substance, which was formerly known as atophan.

Procaine.—This substance was introduced from Germany under the name Novocaine. It is very widely used as a local anesthetic. Probably seventy-five percent of that sold is used by dentists for the extraction of teeth and for other dental operations. When we began the manufacture of this product, I had the belief—which I presume is shared by most of you—that a very large amount was employed by physicians. Strangely enough, only relatively little of it is used by the medical profession—a fact which is greatly to be regretted because it is a substance which can be employed easily, safely and profitably in thousands of cases in which operation is performed at the present time under ether or chloroform, or, worse yet, with no anesthetic at all. Such men as Crile of Cleveland and Harris of Chicago are warm advocates of its use in the method of anesthesia called variously "anociassociation" or "nerve blocking."

Procaine is a very expensive drug to produce, but the price is going steadily downward; it is sold, in quantity, at the present time much more cheaply than it was ever sold by the Germans before the war. Licenses were issued for its manufacture to H. A. Metz & Company, the Rector Chemical Company and The Abbott Laboratories. The present status of its production by the Rector Chemical Co. I am unable to give you, because of certain changes in organization which have taken place in that house. The largest producer is Metz. The quantity sold can only be estimated, but I believe it cannot exceed 3000 pounds a year.

Luminal is manufactured only by the Winthrop Chemical Company which operates under the patent owned by Bayer.

Anesthesin is manufactured by The Abbott Laboratories and by H. A. Metz & Co. Its use is increasing. This drug is an effective anesthetic in powder form, and, being insoluble, is of only very low toxicity and therefore can be used safely orally and as a local application. Large quantities are being manufactured into troches and lozenges for the treatment of cough and relief of pharyngeal irritation. It is also being employed in increasingly large quantities in various dusting powders. Anesthesin is a side product in the manufacture of procaine.

Of the other items mentioned I can give so little information concerning manufacture, prices and quantities produced that I shall omit further reference to them.

New Products.—Few physicians or pharmacists realize how much research work has been done in this country by manufacturers of pharmaceutical chemicals during and following the war nor can they understand how great the promise is in this field, providing reasonable protection is given to this industry during the next decade. For instance, "research laboratories are expensive to maintain. It is only through these laboratories that new substances may be discovered which will make America independent of foreign sources of supply." Permit me to call attention to a few of the things which have been accomplished by American firms during the last few years.

During the war, Browning and others in England showed that certain dyes, particularly the flavines and brilliant green, had peculiar value as antiseptics. Of these the flavines (acriflavine and proflavine) are the most valuable. The manufacture of these was not undertaken in the United States until after the close of the war. These are now produced by the Heyl Laboratories, the Van Dyk Company and The Abbott Laboratories. The synthesis of the flavines is exceedingly difficult, involving many steps and great expense in the production on an industrial scale. In spite of its high price acriflavine is being used in increasingly large quantities, particularly in the treatment of gonorrhea for which it has certain well-marked advantages. Recently E. G. Davis, of the University of Nebraska and Johns Hopkins University, has shown that acriflavine, taken internally, is an effective urinary antiseptic. He tested it experimentally in comparison with some 400 other remedies, and found it the best of all those which he tried. It is also being used in a very limited way intravenously for the treatment of various septicemias.

A product somewhat similar in action, and likewise a dye, which has been developed in this country mainly since the war, is mercurochrome, manufactured and sold by Hynson, Westcott & Dunning, of Baltimore. It is also used mainly in the treatment of gonorrhea

In the field of local anesthetics, Parke, Davis & Co. have produced apothesin, which chemically is the g-diethyl propyl alcohol ester of cinnamic acid. It is giving good satisfaction and is already being widely used.

A substance which has been developed as a local anesthetic is saligenin, which has been brought to the attention of manufacturing chemists and the medical profession by Prof. A. D. Hirschfelder of the University of Minnesota. Chemically it is salicyl alcohol. It is being manufactured by the Calco Chemical Company and by The Abbott Laboratories.

Benzyl alcohol has likewise been suggested as a local anesthetic, and is being used to a limited degree. This is the work of Prof. David I. Macht of Johns Hopkins University.

The Abbott Laboratories has introduced a new local anesthetic under the name butyn. Chemically this is the sulphate of p-aminobenzoyl gamma-di-n-butylamino propanol. So far as we know, this is the first local anesthetic introduced primarily to replace cocaine. It has the advantage of being at least twice as anesthetic as the latter substance, being more rapid in action, giving more prolonged anesthesia, causing no irritation, being stable on boiling, and being slightly antiseptic, and non-narcotic. It is the invention of Professors Roger Adams and Oliver Kamm of the University of Illinois and Dr. E. H. Volwiler of the Abbott Laboratories. The product will be referred to again.

A notable discovery, not distinctly in the synthetic field but yet in a line closely allied to it, was that of thyroxin, the active principle of the thyroid gland. This was made by Dr. E. R. Kendall, of the Mayo Foundation. The prediction is made that this will eventually be made synthetically. This substance is probably much more valuable than anything heretofore known for increasing metabolism in diseases caused by hypothyroidism. It has recently been placed on the market by E. R. Squibb & Co.

A very interesting discovery, made by Dr. David I. Macht of Johns Hopkins University, was that benzylbenzoate, a substance heretofore known principally to perfumers, was in reality a powerful antispasmodic. Benzylbenzoate has opened a new field; although it has at times been disappointing in practice, its study has led us into some very interesting research work, to which I will refer later.

The Difficulties of Original Research.—Few realize the difficulties involved in putting out a new or even an old synthetic chemical. When the work in the chemist's laboratory is finished, or seems to be finished, the trouble has only begun, because the production of chemicals on an industrial scale involves the handling of larger quantities, under varying conditions as regards temperature, pressure, etc., and the question of yield immediately becomes vital, for if a sufficient yield is not produced not only from the final step, but at every step in the course of production of one of these finer chemicals, its manufacture in a commercial way becomes impossible.

In elaborating a new product, the work of the chemist has to be done over and over again. You all remember the classic experience of Ehrlich, who was only able to produce salvarsan after 695 ineffectual attempts.

I have referred to butyn, the new local anesthetic which The Abbott Laboratories is just now placing on the market. Before we were able to produce this substance we made about forty new chemical bodies. Most of these were carefully tested upon animals. A number of them had merit as local anesthetics, but until butyn was reached none was found which presented decided advantages over anesthetics already available.

I may say in passing that before the war butyn would have been impossible of manufacture, because butyl alcohol, one of the most important intermediates in its production, was practically unknown and procurable only at a prohibitive price. It was a curiosity. Its commercial manufacture grew out of the synthetic production of acetone, which was required as a solvent for the making of explosives.

In the production of a new chemical like butyn the closest collaboration between the chemical laboratory, the pharmacological laboratory, the physician, and the industrial producer is essential, in order to get satisfactory results in a reasonable time. No synthetic product heretofore produced in this country has been the result of such favorable collaboration between these different agencies. The chemical work on it was done in part in the laboratories of the University of Illinois and in part in our own laboratories. The pharmacologic work was undertaken primarily by our Mr. Nielsen, and then was taken over and carried through exhaustively by a pharmacologist in one of our leading universities. The clinical work was done in part in private practice by Dr. Harry S. Gradle of this city and by about 100 other physicians and dentists, and in part by the Research Committee

of the Section of Ophthalmology of the A. M. A., under the direction of Dr. Albert E. Bulson, Jr., of Fort Wayne, Indiana. We base our claims for this product upon the collective work of these various groups.

In this connection I wish to refer briefly to a new product which stands in the same relation to butyn as anesthesin does to procaine. I mean butyl *p*-amino benzoate, which for convenience we are calling butesin. This local anesthetic was invented by one of our chemists some two or three years ago. The preliminary tests showing that it had merit, it was submitted to Dr. A. S. Loevenhart of the University of Wisconsin for pharmacologic research. His report showed that it was more powerful than anesthesin, and its action about six times as prolonged. It is insoluble in water, and according to preliminary investigations practically non-toxic. As a matter of protection it was patented, but in view of other extensive and more promising research, no effort was made to have it tested out clinically. About three months ago we were notified that our patent would be contested by the Societé des Usines du Rhone, the largest manufacturing chemical house in France. This concern has already patented this chemical in France, Germany, Switzerland, Italy and Great Britain. Fortunately we have been able (we believe) to prove priority in the United States. This illustrates how easily our expenditures for research may be nullified.

An exceedingly interesting research has been carried on in our laboratories on the benzyl esters, in an effort to find an antispasmodic superior to benzyl benzoate. We have made a large number of these esters, the most important being benzyl succinate, benzyl stearate, benzyl phenolate, benzyl cinnamate, benzyl fumerate, benzyl salicylate, and benzyl acetylsalicylate. In addition to their manufacture, a series of hydrolysis tests was carried out with these esters, to ascertain if possible whether the rate of hydrolysis had any relation to the physiologic action of the drug. All of these esters were then exhaustively tested pharmacologically upon cats and dogs, the method employed being one devised in our own pharmacologic laboratories. The results of this research were published in *The Journal of the American Chemical Society* and in the *Journal of Laboratory and Clinical Medicine*. They seem to show that of these esters two, *i. e.*, the fumerate and the acetylsalicylate, possess outstanding merit. Before committing ourselves, it will be necessary that the drugs be tested clinically. Only a limited amount of such work has been done with these preparations as yet. In the meantime, other new benzyl esters heretofore unstudied are being made. We hope that as the result of this work something of value may be evolved.

Expense of Research.—Few people realize how expensive it is to "discover" and put on the market a new synthetic chemical. At the present time, in the United States, the manufacturer who wishes to go into this field must take a gambler's chance. The Abbott Laboratories has been willing to take this chance because it believed that the future of any pharmaceutical firm depends upon its ability to measure up to the spirit of the times and bring its business into accord with the changing and developing tendencies of the age. Thus far we have been satisfied with the result, but we are free to confess that we cannot plumb the future. Our own experience has been that to develop a purely synthetic medicinal chemical, involving what we may call an average degree of difficulty for one of the finer preparations of this class, means a cash outlay of from $25,000 to $50,000. I

mean that every dollar of this amount will be put into the product before a dollar comes back. This expenditure is for research only; but by "research" I mean not only the money spent by the chemist and pharmacologist but also the outlay involved in turning out the product on an industrial scale. Before we learned wisdom by experience, we have seen some thousands of dollars go down the sewer when a reaction went wrong.

The question will arise in your mind whether expenditures like this, and risks like these, for indeed they are risks, are really worth while. We believe they are, because, as we have already said, the future of this country in the medical field, as well as in industry, is going to depend very largely upon the collaboration between the chemist and the other fellow, and in this case the other fellow is the physician, the pharmacist, and the clinic. In thinking about this collaboration, it is important that we should consider how we can utilize all our latent forces. Germany acquired prominence in the medical field because the German government was quick to realize the importance of the chemical industry in both peace and war. There was brought about a closely interwoven and mutually profitable relationship between the universities, the therapeutic research organizations, hospitals and clinics, and the manufacturing houses. Say what you will about the Germans, they did not cut each other's throats, and they did not encourage foreigners to come in and scuttle the ship. Their protection was skilful, but absolute. It was external as well as internal. They not only made the goods, but they went out and got the markets.

I do not advocate the adoption of the German method in this country, but I know that as far as research is concerned it is vitally important that our universities, which are now as finely equipped and turning out as good men as other similar institutions in the world, should receive the best kind of encouragement—the assurance that their graduates will get jobs when they are through, and this can only be accomplished by the protection of the manufacturers who are undertaking to risk their money in a business which, to say the least, is a precarious one. Research in the universities and such scientific institutions as Rockefeller, Sprague, McCormick, Mayo, Brady and other institutes must be linked with research in the manufacturing houses themselves. Further, even the richest of our great research institutions are handicapped by lack of endowment. The manufacturer will not hesitate to spend $50,000 or more a year in research if there is a reasonable prospect that he will get a run for his money; but $50,000 a year is the interest on an endowment of a million dollars—and how many universities or other purely research organizations can afford to set aside a million dollars simply for the study of a single drug, which may or may not be valuable when the work is done?

As an illustration of what is being done by the greatest of our research institutions, The Rockefeller Institute, let me quote from a pamphlet entitled "The Future Independence and Progress of American Medicine in the Age of Chemistry," written by Abel, Alsberg, Bacon, Eldred, Hunt, Johnson, Stieglitz, Taylor and Herty, and published by the Chemical Foundation:

"The largest and most prominent of these institutions," this pamphlet states, "is the Rockefeller Institute for Medical Research. The staff of this institute consists of ten 'members' with their associates and assistants. Eight of these 'members' are occupied with studies on bacteriology, pathology, immunology, serology,

general physiology, diseases of animals, experimental surgery, clinical researches on diabetes, heart disease, kidney disease, pneumonia, yellow fever, meningitis, infantile paralysis, etc. In the fall of 1920 announcement was made that during the ensuing year the following diseases would be made the subject of special study at the institute: acute lobar pneumonia and other acute pulmonary infections, measles, acute rheumatic fever, cardiac disease and nephritis.

"Two 'members' devote their time to chemical work. The activities of the one relate largely to the structural chemistry of nucleic acids, lipoids, and other important components of the body. Under this 'member,' also, are chemists whose work relates to chemotherapy; their researches have extended to such compounds as derivatives of hexamethylenetetramine, of certain arsenic acids and of quinine. A number of these derivatives have been tested in other divisions of the institute and in the hospital, for their therapeutic action. The other chemical 'member' works in connection with the hospital of the institute and his work at present relates chiefly to refinements in the methods of blood analysis and other methods of clinical interest. A third 'member' of the institute is working on the fundamental theory of colloids and the application of other physical relations of life phenomena. Part of the excellent work of this institute is in the direction of our chief aims, but the emphasis is rather placed on the pathological and other medical features of the problems than on the direct attack on the problems of medicine by means of a concerted, wholly coöperative effort of leaders in the fundamental sciences of chemistry and physics, in pharmacology and in medicine."

This quotation shows not only that the Rockefeller Institute is doing magnificent work, but that even the fine endowment available is only sufficient to scratch the surface from the chemical point of view. Compare the methods employed in this country to develop chemical knowledge in medicine with those prevailing in Germany. We find that in the latter country there is the most complete possible collaboration covering the whole scale and ending only with the manufacturer, who works hand in hand with the research institute, the clinic, and, most important of all, the government.

In our establishment we are seeking contact with the best scientific minds of the country. We try to get acquainted with and keep in touch with the work of the brilliant research men who prefer to teach, and should be encouraged to teach. We believe that here is a great mine which can be developed not only for our profit, but to the benefit of the entire country.

Following this contact on one side with the chemists, we are anxious to develop the other side, closer contact with the clinical resources of the country, because progress in medicine commensurate with the greatness of this country is only possible by coöperative utilization of our undeveloped resources in brains. The achievements of the last few years, of which we are all justly proud, are due largely to the fact that we were forced to cut loose from the apron strings of German science. We found we could walk alone, and some of us now think we might grow up; but there are people in the United States who still believe that only the Germans know how to make dyes and drugs, and that we should return humbly to our former condition of scientific dependence. Such a surrender then—for surrender it will be—means setting back the hands of the clock so far as the progress of American medicine goes. It means that we shall be unable to contribute our proper

share to the scientific work of the world during the next generation. It means that medicine will not develop in this country as it will elsewhere in the world, where chemical sciences are recognized as being fundamental to a knowledge of the human body in health and disease and to the maintenance of the public welfare.

I appeal to you gentlemen, whose interests are closely allied with those of the chemical manufacturer, for support at this critical time which means so much to the future of this, our common country.

VITAMINES, AN INDISPENSABLE NUTRITIVE GROUP.*

BY M. F. WILSON, M.D.

The subject of the vitamines is of particular interest to the pharmaceutical profession, due to the fact that it presents not only the most recent advance along pharmaceutical lines of the last few years, but also due to the fact that the vitamines are the most frequently discussed subject in medical literature, as well as among the lay magazines and the daily press. Over 110 papers have appeared in the last three years in medical literature upon this subject, and in our newspapers, under public health columns, the subject is mentioned almost daily. Only a short time ago, a celebrated writer suggested the possibility that in the near future we would have a shaker containing extract of the vitamines alongside of our salt and pepper cellars, in order that we might apply the extract to our food rations to make up for the deficiency.

It is only in later years that this substance has been studied with any degree of accuracy, but clinicians and pathologists have long known that there were certain diseased conditions arising in the course of their studies which could not be traced to any then known etiology. Most of these conditions can now be classed under the heading of "Vitamine Deficiency" diseases. Jack London, in his story of "The Tale of the North," recites an incident where the early pioneers in the Alaskan region were affected during the winter months with scurvy in which they found that the eating of raw potatoes was curative. He states that when this fact became generally known this article of diet increased in price to such an extent that it became a bankable commodity. In the light of the present knowledge we know that potatoes simply supplied the lack of vitamines and brought about a cure in this way.

During the last war in certain regions of the old world, particularly in Denmark, children who were fed upon the so-called centrifugalized milk and "export" cream developed a variety of peculiar but characteristic symptoms, but upon the feeding of these infants with whole milk and cod-liver oil containing vitamines, they rapidly improved and soon became normal.

The beginning of the scientific study which ultimately resulted in the isolation of the extract of the vitamines dated from the Japanese-Russian war. Sailors of the Japanese navy were attacked with a malady called beri-beri or polyneuritis. Hundreds of these men were affected, suffered agonies and resulted in the death of many. The disease was characterized by soreness in certain sets of the muscles, gastric disturbances, loss of power in the muscles of the legs, heart ir-

* A brief extract from an illustrated lecture delivered before Section on Practical Pharmacy and Dispensing, A. Ph. A., New Orleans meeting, 1921.