

PROGRESS IN MEDICINE AND PHARMACY.*

BY JOHN F. ANDERSON, M.D.¹

"I am glad to have the pleasure of addressing the Northern Ohio Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION and of discussing before you some of the developments of the past few years in medicine and pharmacy. The practice of medicine and pharmacy is a very different thing from what it was when I graduated in medicine some 25 years ago. With a few exceptions, like quinine in malaria and mercury in syphilis, the treatment of disease was then largely based upon the empiric use of drugs or methods. The new sciences of pharmacology, biochemistry, chemotherapy, bacteriology and immunology were just coming into prominence as powerful allies and supports of scientific medicine. As a result we were acquiring our first definite knowledge of the treatment of disease based upon sound research in the laboratory and at the bedside. Since then there have been rapid strides toward the goal of the specific treatment and prevention of diseases, not only among those of infectious origin, but also among those caused by a failure of the proper functioning of the important organs of the body.

"The science of bacteriology made the first great advance in the specific treatment and prevention of disease when von Behring and Roux, following the trail so clearly blazed by Pasteur and Koch, announced the discovery of tetanus antitoxin and of diphtheria antitoxin. Before diphtheria antitoxin came into use, one in every three children who developed the disease died. Tetanus antitoxin made it possible to prevent many deaths with the horrible and painful symptoms of lock-jaw.

"The epoch-making discoveries of Roux and of von Behring opened to us the vista of the eventual control of other diseases caused by bacteria. Unfortunately, this hope has been slow in being realized. The next great advance was not made until 28 years later, when came the discovery by Drs. George F. and Gladys H. Dick of the cause of scarlet fever, its prevention, diagnosis and treatment. The Dicks' discoveries were first published in 1923, and have made it possible to apply with confidence specific means in the treatment and prevention of scarlet fever of which there occur annually in the United States more than 200,000 cases.

"It has just been stated that prior to the work of the Dicks on scarlet fever, an interval of 28 years elapsed without the discovery of a single antitoxin of major importance. During this period, naturally, an enormous amount of work was done in an effort to acquire control of scarlet fever. You wonder why all this work was sterile as far as the production of positive results, while the Dicks were so phenomenally successful, and you probably rightly suspect that they introduced a new principle or a new technical method into the study of scarlet fever. Most of the work on scarlet fever has been done on laboratory animals. The Dicks came to the conclusion that laboratory animals were not susceptible to scarlet fever. When they suspected that the cause of scarlet fever was a streptococcus, they tested this hypothesis not on guinea-pigs, but on human volunteers. They produced typical scarlet fever in a young man by spraying his throat with a streptococcus obtained from a case of scarlet fever. They thus demonstrated beyond question that a streptococcus was the cause of scarlet fever. And the same principle was used when they wished to determine whether the scarlet fever streptococcus produced a toxin. The toxin of the scarlet fever streptococcus is characterized by the fact that it is without effect on laboratory animals. In this respect it is distinguished sharply from the toxins of the diphtheria and tetanus bacilli. The standardization of the scarlet fever toxin and scarlet fever antitoxin must therefore be done by means of skin tests in susceptible human beings. This is a matter of some inconvenience to those interested in the preparation of scarlet fever products, but this inconvenience is mitigated by the realization that scarlet fever antitoxin would still be undiscovered unless the Dicks had used the method of skin tests in human beings for its study.

"Even before the use of scarlet fever antitoxin in the treatment of scarlet fever, the Dicks were able to show that antitoxin would probably be effective in the treatment of the disease. The fact that it neutralized scarlet fever toxin demonstrated this to some extent; but they showed further that the injection of a minute amount of antitoxin into the skin of a scarlet fever patient

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caused the disappearance of the rash at the site of injection. This is known as the blanching test, and it is useful in the diagnosis of doubtful cases of scarlet fever.

"Scarlet fever antitoxin is now available in a concentrated and purified form, comparable to the concentrated diphtheria and tetanus antitoxins. Its effect in scarlet fever can best be realized if I quote briefly from a recent paper by Dr. Edwin H. Place of the Harvard Medical School (*Jour. of the Medical Society of New Jersey*, Feb. 1929). 'After the injection of scarlet fever antitoxin the rash subsides with great rapidity, usually within 24-48 hours. It is often impossible to make a diagnosis 24 hours after antitoxin has been given. The throat symptoms, if unaccompanied by membrane and swelling, subside as rapidly. In surgical scarlet fever, the improvement is often miraculous; not only do the toxic symptoms subside rapidly but the severe advancing wound infection rapidly clears. Unfortunately, this does not always occur; but as a rule this group of infected wound cases, including the puerperal state, constitutes the most striking exhibit of the life-saving value of scarlet fever antitoxin.'"

"The Dicks also showed that the injection of a small amount of scarlet fever toxin into the skin of susceptible individuals caused the development of a red area. This is known as the Dick Test, and by its means we are enabled to detect individuals who are susceptible to scarlet fever. The Dicks further showed that susceptible individuals may be vaccinated against scarlet fever by the injection of increasing doses of scarlet fever toxin. Since prevention is better than cure, this prophylactic immunization against scarlet fever is perhaps to be regarded as their greatest discovery.

"The Dicks applied for a patent on their discoveries, which was granted in July 1925, in order that they might have control over the methods of production, dosage used and of standardization. The patent is administered by the Scarlet Fever Committee which has granted licenses to certain biological manufacturers for the production and sale of scarlet fever products under the control of that Committee. Products so produced have an additional control of their potency over that of the manufacturer and of the Government, which is an added guarantee that they are dispensed in the proper form and dosage, and may be relied upon to exert their full specific effect.

"Very soon after the discoveries of the Dicks, Dr. Birkhaug of the School of Medicine and Dentistry of the University of Rochester, Rochester, N. Y., announced that the streptococcus of erysipelas produced a toxin, and that a specific antitoxin could be prepared with this toxin. Erysipelas antitoxin is used extensively in the treatment of erysipelas, and is to be considered one of the outstanding discoveries of the past decade. According to Symmers and Lewis, who have had extensive clinical experience with erysipelas 'the antitoxin treatment of erysipelas marks an advance, the results of which are commensurate with those obtained in the treatment of diphtheria.' They state further that as far as the immediate attack is concerned, erysipelas is now a vanquished disease.

"Recent discoveries in regard to diphtheria have had to do almost entirely with the prevention of this disease. Von Behring, the discoverer of diphtheria antitoxin, first showed that the injection of a mixture of diphtheria toxin and diphtheria antitoxin produced immunity against the disease. This method was subsequently studied and standardized by Dr. William H. Park and his associates of the New York City Department of Health. The injection of three doses of toxin-antitoxin at weekly intervals has been repeatedly shown to immunize the individual against diphtheria.

"Diphtheria toxin-antitoxin is playing a larger and larger part in the prevention of diphtheria. The campaigns of education that have been carried on by the various health departments have been markedly effective, and parents now are generally acquainted with the fact that toxin-antitoxin is effective protection against diphtheria. Recently toxin-antitoxin has been still further improved by preparing it from concentrated antitoxin obtained from the sheep instead of the horse. This change was made because there is no possibility that sheep serum will sensitize the individual to subsequent injections of therapeutic serum from the horse, should these be necessary in later life.

"Another preparation called Toxoid is also used in the preventive immunization against diphtheria. Toxoid has been studied particularly by Dr. Ramon of the Pasteur Institute in Paris. Ramon found that if a small amount of formaldehyde is added to diphtheria toxin, the toxin lost its toxicity without destruction of its immunizing properties. Toxoid is used in the same manner as toxin-antitoxin. Toxoid has the advantage that it contains no foreign serum whatever.

It has been extensively used in France with the most satisfactory results. Many health officers in this country are now interested in determining whether toxoid is superior to toxin-antitoxin.

"It must be mentioned that manufacturers of biological products have made marked progress in the past 10 years in the concentration of antitoxins and serums. The progress here has been gradual and, for that reason, perhaps, has not been fully appreciated by the medical and pharmaceutical professions. This concentration has led to a much lower incidence of anaphylaxis and serum disease.

"Strange as it may seem to us now, it was at first supposed by many that these reactions of anaphylaxis were brought about by the antitoxin itself. It has been definitely shown, however, that the reactions are due to inert proteins present in all serum. The removal of a large part of these inert proteins during the process of concentration has resulted in a marked reduction in the incidence of these undesirable reactions and has given to modern physicians a degree of confidence in the safety and efficacy of antitoxins not possessed by physicians generally in the early days when only crude unconcentrated preparations were available.

"For some years prior to the World War, vaccination against typhoid fever had been required of all officers and men of our Army and Navy. Medical officers of both services were fully acquainted with its efficacy in preventing typhoid fever. It had not, however, attracted much attention as a means of preventing typhoid fever in civil life. During the past several years, however, an ever-increasing interest has been shown in typhoid vaccine by members of the medical profession in civil life. The army statistics of the World War have been most convincing in regard to the prophylactic value of typhoid vaccine. The layman, with his present keen interest in preventive medicine, frequently requests that his physician immunize him against typhoid fever, particularly whenever he may be exposed to infection, as on vacation trips. This popularization of typhoid vaccine is an advance of great potentialities in the saving of life and the prevention of sickness.

"Perhaps a few words should be said here about non-specific therapy. By this is meant the treatment of disease, not by a specific agent, but by some substance capable of producing a general reaction in the body in the hope that this reaction will aid in overcoming disease. Typhoid vaccine, milk, nucleic acid and a host of other substances have been tried with varying degrees of success in the treatment of diseases such as chronic arthritis. Possibly these methods of treatment are already beginning to pass into disuse. There remains, however, one outstanding success of non-specific therapy. I refer to the treatment of paresis with malaria. Paresis, as you know, is a late stage of syphilis, in which the cerebral cortex is attacked with the production of mental and physical abnormalities. Many of these patients led useless lives for a period of several years and always eventually died. Now these patients are artificially inoculated with malaria, another infection, and are allowed to pass through several febrile paroxysms. After this, the malarial infection is easily cured with quinine. Many paretics so treated are now leading active useful lives.

"The science of chemotherapy was founded by Paul Ehrlich. It was the aim of this new branch of knowledge to discover compounds with a selective toxic affinity for invading micro-organisms and a relative low toxicity for the host. Everyone is acquainted with the brilliant researches which led to the introduction of arsphenamine in the treatment of syphilis, followed soon by neoarsphenamine. The most recent addition to the arsphenamines is sulpharsphenamine. This newer compound is especially suitable for the treatment of certain cases of syphilis, since it can be given intramuscularly in highly concentrated form. It also seems to be more uniform in its composition than neoarsphenamine, and more stable.

"In recent years much attention has been given to the chemotherapy of bacterial infections. This has resulted in the accumulation of a vast amount of useful information regarding certain antiseptics, particularly of dyes, such as gentian violet. Unfortunately, however, there has not been a single notable contribution in the chemotherapy of bacterial disease. It is doubtful to many workers whether any of the newer germicides have advantages even as a skin disinfectant over the time-honored tincture of iodine.

"In the closely related science of pharmacology, ephedrine is undoubtedly to be regarded as the outstanding achievement of recent years. The Chinese have used decoctions of a plant called mahuang in medicine for over 5000 years. Ephedrine, an alkaloid, is the active principle of this drug. It has an effect in the animal body very closely resembling that of epinephrine.

Its action is considerably slower, but it has the advantage that it can be taken by mouth and that the period of its physiological activity extends over a longer time. Ephedrine has proven of distinct value in the treatment of hay fever and asthma. We are indebted particularly to K. K. Chen for our knowledge of the pharmacology of ephedrine.

"In 1921 Maurice Hall discovered that carbon tetrachloride was efficacious in the treatment of hookworm disease. This valuable remedy now supplements thymol and oil of chenopodium in the treatment of this scourge of tropical and subtropical countries.

"In no field of medical research have the results been more brilliant or of greater value than in Endocrinology or the science of the internal secretions. We now have as many as 6 preparations from the organs or fluids of the animal body the value of which has been proved in conditions due to the lack of the essential principle, or hormone, of a gland of internal secretion.

"The first of these hormones was epinephrine from the suprarenal gland, the isolation of which in pure form was announced by Abel and Crawford in 1897. Since then we have had pituitary solution from the posterior lobe of the pituitary gland, thyroxin from the thyroid gland, insulin from the pancreas, parathyroid extract from that gland, and the female sex hormone which induces estrus.

"Thyroxin was obtained in pure form by Kendall in 1915, and found to have the same physiological properties as desiccated thyroid gland. It is possible by the use of thyroxin to employ more exact dosage and to avoid the variation in activity sometimes found in the desiccated thyroid. Further, it was determined by the intravenous administration of crystalline thyroxin that quantitative response within close limits could be obtained. In other words, the isolated hormone has the advantage of a pure principle over the crude material. Thyroxin is used for all those conditions due to a deficient secretion of the thyroid gland.

"All of you well know the hopeless outlook for a case of diabetes, particularly if under 20, before insulin first became available in 1923. It has been estimated that there are as many as 1,000,000 cases of diabetes in the United States, many of whom without insulin might expect an early death from diabetic coma. Insulin was discovered by Macleod, Banting, Best and Collip of the University of Toronto, and the patent granted them is administered by the Insulin Committee of that University. A limited number of licenses have been granted for the manufacture and sale of insulin under such control as will insure a product meeting their requirements. Some licensees have given much time to research for the development of improved methods for the preparation of insulin, so that the product as now available possesses many points of superiority over that first used. Especially have there been improvements in clarity, stability, uniformity and accuracy of standardization, freedom from reaction producing proteins and absence of pigimentary impurities.

"The last of the hormones to which reference will be made is the one variously designated as the female sex hormone, ovarian hormone and other names. The first preparations of this hormone were made from the entire ovary, but as a result of research in many laboratories it has been recovered from other parts of the female body and especially from certain fluids. In this respect the estrus-inducing hormone obtained from these various sources parallels insulin which may be obtained from organs or tissues other than the pancreas and which is identical in its physiological action when so obtained. The ovaries, in addition to being the reservoir for the ovum, also produce an internal secretion or hormone which is necessary for the proper functioning of the uterus and which also has effects upon metabolism and the nervous system. The lack of this hormone after puberty and until the menopause is well established is frequently attended with symptoms of a definite and often distressing nature. Various preparations of the ovary such as tablets, extracts, powder, have for years been used in the treatment of conditions attributed to ovarian hypofunction without, however, very definite results from their use. These preparations were not standardized and there were no tests available for quality or identity. Almost all were intended for oral administration.

"As a result of the work of investigators for the past 10 years, it has become possible to prepare a sterile aqueous solution of the estrus-inducing hormone, potent and physiologically standardized.

"American investigators have been prominent in the study of this hormone, among them being Allen, Doisy, Stockard, Papanicolaou, Long, Evans, Frank, Novak, Loeb, Pratt, Morrell and Powers.

"Doisy, Ralls and Jordan have outlined as the requirements of a satisfactory preparation of the estrus-inducing hormone the following:

1. That the hormone be dissolved in an innocuous, aqueous medium.
2. That it be assayed by the smear method.
3. That it be ampuled to contain 5 to 10 Rat Units per 1 cc.
4. That ample tests of its sterility and keeping qualities be made.
5. That it should have no effect upon the blood pressure of anesthetized dogs.

"A preparation meeting these conditions prepared from the amniotic fluid of cattle is now available under the name of Amniotin. In addition to its ability to induce estrus in spayed white rats it will also induce menstruation in spayed rhesus monkeys. Just as insulin, it is given by hypodermic injection. It is used in the various conditions associated with ovarian hypofunction and for palliating the symptoms of artificial or natural menopause.

"Mention should be made at this point of the discovery of Minot and Murphy of the value of liver and extracts of liver in the treatment of pernicious anemia. This discovery was a development of the work of Whipple and his associates. Previous to the use of liver the outlook for pernicious anemia was almost uniformly hopeless.

"This brief review of the advances in medicine and pharmacy would be very incomplete unless reference is made to the knowledge that has come to us in the past ten years of those mysterious principles or agents known as vitamins. Vitamins are substances which though present in minute quantities in foods are absolutely essential to the continuation of the life process. The deficiency diseases are the result of an insufficient amount of vitamins and are so named because of the lack of something in the diet. We are not able to say whether they exert their action as essential tissue components directly on the tissues or, as has been suggested by someone, through a hormone action. Possibly both of these views are correct. It appears that vitamin A is an essential factor in the normal chemical processes of all epithelial cells, and that vitamin D exerts a hormone action in mineral metabolism. They are chiefly produced as a result of the vital process of the lower forms of life, and have been grouped according to their solubility, that is, fat-soluble and water-soluble.

"Concerning these important principles, McCollum has stated that 'many continue to believe that common experience has shown the safety of allowing the appetite, financial means and custom to be the guide in the selection of food.' The discoveries of the existence of hitherto unknown food principles, and the biological assay of all of our more common food stuffs by approximately planned feeding experiments, have brought to light a number of specific kinds of malnutrition. These can be produced at will in animals; they are so strikingly like diseases which have long existed among human beings in certain places that they suggested the cause of the latter. The results of applying the knowledge of quality in foods to the study of human diseases has demonstrated that faulty diet has been and is the cause of much physical inferiority, illness and early mortality in infants and children: it has also been shown that careful attention to the food supply of the sick affords an effective means of cure in certain conditions and of relief and the extension of life in others."

There are five of these vitamins concerning which our knowledge of their source, action and use is definite. These vitamins are now designated as A, B, C, D and E, and each and all of them are essential to health.

Vitamin A is necessary to growth. Its absence is followed by a keratinization of the epithelial cells in all the tissues of the body. This keratinization is characterized by a change to a dry, chemically inactive type of cell which quickly falls prey to invading bacteria. It is found most abundantly in cod liver oil, butter fat, egg yolk, liver, leafy vegetables and yellow pigmented vegetables.

Vitamin B (the absence of which results in the development of beri-beri and also thought by Goldberger to be concerned in the cause of pellagra) contains two different principles—one known as the anti-neuritic factor and the other the p. p. factor. Vitamin B is most abundant in eggs and in cereals such as wheat and in yeast. A palatable form of vitamin B has been made from the germ of wheat. This preparation in addition to being a very concentrated form of vitamin B is of value in the modification of milk for infants on account of its dextrin-maltose content. Although very little beri is seen in the United States, recent researches in pediatrics have shown that infants in particular frequently suffer from vitamin B deficiency. This has

been recently emphasized by Hoobler (*J. A. M. A.*, 91 (Aug. 4, 1928), 307) who believes that a substance rich in vitamin B should be regularly prescribed for the infant dietary just as cod liver oil and orange juice are prescribed. This is particularly the case since neither human milk nor cow's milk are dependable sources of vitamin B.

"Vitamin C is the vitamin responsible for protection against scurvy, and is particularly abundant in orange juice and in certain fresh vegetables such as cabbage, carrots and tomatoes.

"Vitamin D is the anti-rachitic factor and controls the calcium-phosphorus metabolism of the body. In addition to its influence over growth, it is also effective in the proper development and growth of the teeth and bones. Its absence leads to the condition known as rickets. The most abundant source of the antirachitic factor or vitamin D is good cod liver oil. It is also found in butter, eggs and certain of the green vegetables. Curiously enough it has been found that the rays of the sun have the same action as this vitamin, also that the ultraviolet rays have this property which they can in turn transfer to certain other substances—thus conferring upon these substances an anti-rachitic action.

"In addition to the four vitamins just referred to there is also vitamin E which by some is thought to have an influence upon sterility and lactation.

"Our knowledge of the vitamins has increased the number of specific remedies in disease. Vitamin B, for instance, is a specific for beri-beri and certain types of marasmus in infants; vitamin C is a specific against scurvy, and vitamin D is a specific for rickets. The effect of vitamins in the treatment of these diseases is nothing short of spectacular. All four vitamins are probably concerned in resistance to infectious diseases. You can readily see, however, that the greatest good of our knowledge of vitamins will be accomplished by their prophylactic use. The coming generations will suffer much less from deficiency diseases than the present.

"This brief review of the developments in medicine and pharmacy of the last few years will serve the purpose of refreshing your knowledge of these developments and emphasizing that none of them have been made possible except as a result of patient research by workers in all parts of the world both in the laboratory and at the bedside. These developments in the prevention and treatment of disease have almost revolutionized the practice of medicine and pharmacy, yet nevertheless are probably to be regarded as the precursors of still more important progress in the immediate years of the future."

PROPOSED SURVEY OF THE DRUG TRADE.

Representatives of the industries and associations of the drug-trade activities met with representatives of the U. S. Department of Commerce to discuss a proposed survey of the drug trade, on January 20th. The meeting was called by Robert L. Lund, of St. Louis, for the purpose of discussing the desirability of petitioning the U. S. Department of Commerce to make a survey of the drug business, similar in import to the survey of the retail grocery business recently completed by the Department of Commerce in Louisville, Ky. It was the final decision of the group assembled that a petition should be presented to the Secretary of Commerce for such a survey and that the survey be made in and of the drug business of the City of St. Louis.

R. L. Lund was named Chairman of the meeting, and E. F. Kemp, secretary. Among those present from various organizations were:

From St. Louis, O. J. Cloughly, A. W. Pauley, R. L. Lund, Adolph C. Meyer, A. H. Grosse, W. H. Harper, Theo. F. Hagenow, H. C. Fink,

John M. Drescher; Washington Wholesale Drug exchange, Paul Pearson and W. H. Bradbury; Federal Wholesale Druggists' Association, R. E. Lee Williamson, Baltimore; American Pharmaceutical Manufacturers' Association, H. Sheridan Baketel; AMERICAN PHARMACEUTICAL ASSOCIATION, E. F. Kelly, Secretary; Robert L. Swain and Samuel Hilton; National Association of Boards of Pharmacy, Augustus C. Taylor; Package Medicine Association, Roland Nutt; National Wholesale Druggists' Association, W. L. Crouse; National Association of Retail Druggists, Frank T. Stone; Proprietary Association of America, E. F. Kemp; Flavoring Extract Manufacturers Association, George M. Armor; and others; U. S. Department of Commerce, H. D. Cunn and T. L. Gaukel.

Secretary Lamont, Dr. Julius Klein and others of the Department were pleased with the movement and hopeful of success for such an undertaking. The survey necessitates a study of the many phases of the drug-trade activities, which need not be named—reflection will bring them to mind.