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ADVANCES IN MEDICINAL THERAPEUTICS

BY

Sir HENRY H. DALE, O.M., G.B.E., F.R.C.P., F.R.S.

I think that our successors, viewing the times in which we live from the longer perspective of history, are likely to recognize the first half of the twentieth century as the period in which civilization first began to feel, for good or ill, the full impact of progress in the natural sciences. The application of scientific knowledge and methods to man's common activities and needs can be traced, of course, to much earlier beginnings; but the richness of the nineteenth century's closing decade in major discoveries, of the kind from which science advances with a fresh impetus and in new directions, seems to have caused a sudden acceleration of this process to begin about the turn of the century. In no department of knowledge and practice has this change, since 1900, been more conspicuous or more rapidly progressive than in the general field of medicine. The end of the nineteenth century found medicine still a body of largely empirical knowledge, growing mainly by slow accumulation from the direct study of disease at the bedside and of its results in the post-mortem room—a method which in that century had yielded rich harvests indeed; but these had been rare and had ripened but slowly. In 1900, when I entered upon my own undergraduate clinical studies, experimental research had begun to exercise an influence on clinical practice in certain directions, and especially on some aspects of diagnosis—several decades earlier, indeed, it had had Lister's revolution of surgical methods to its credit—but the relation, in general, between the laboratories and the wards remained one of critical aloofness on both sides. It was possible, and not unreasonable, for the student then entering the wards to receive, as I did, an authoritative warning that it was his duty to forget the teachings of the experimental science of physiology and to accept those of medicine, as still an empirical art. The upward inflexion of the curve of progress in the applications to practice of the results and the methods of experimental science seems, indeed, to have begun later in medicine than in some other directions; but when it came it was to be only the more abrupt in its onset, and the resulting revolution in the fifty years which followed was to be only the more complete. It seems to me, then, that a symposium on "Fifty Years of Medicine," from whatever different angles the separate contributors may approach the subject, must have as a central theme that revolution in its relations with the experimental sciences. This has led medicine not only to draw ever more freely from an ever-widening range of these for its own practical purposes but also, in the process, to be so permeated by their methods as to have become largely an experimental science itself well before the end of the period under review.

When I was invited to deal with "Advances in Medical Science" as my contribution to this symposium it seemed to me, accordingly, that acceptance of such a commission would oblige me to range far and wide over nearly all the changes which have occurred in medicine in the past fifty years, and to make deep inroads into almost all the allotments to other contributors. Even a superficial survey of a field so immense and so inclusive I judged to be beyond the proper scope of a single contribution, and far beyond the competence of a single reviewer. I could have written, indeed, with some knowledge, and with the best of reasons for gratitude, of advances in the general estimate of what medical research is worth and of what it can be expected to do. These have raised its status from that of a spare-time enterprise for the rare and unworldly devotee in 1900 to that of an activity to be encouraged and supported, as a career in itself for a minority having a special aptitude, but also as a desirable item in the experience and the credentials of every aspirant to distinction in clinical teaching and practice as we find it to-day. Any survey of the remarkable changes in that direction, and of their effects in enabling this country so greatly to expand its contribution to the general advance in medical science, would have to recognize the enlightened application of public funds through the Medical Research Council and, later, through the University Grants Committee also, as well as to the support given by great private endowments and organized public appeals to the charitable. All of these have been creations of the past half-century.

My proper task, however, was rather to give some impression of the nature and the extent of actual advances achieved in medical science, under whatever stimulus, since 1900; and the only practicable way of attempting this seemed to be to select for review, by way of illustration, the changes which have taken place in one of its major aspects. The developments in medicinal therapeutics seemed likely to serve this purpose particularly well; I doubt whether the change in the half-century in any department has been greater or more fundamental than in this. The interests of the laboratories and the wards seem here to have been even more widely divergent in 1900, and to have since become even more closely identified, than in most other aspects of medicine. I decided accordingly to limit my contribution to a consideration of "Advances in Medicinal Therapeutics"; but I am aware that, even so, there are likely still to be many points of common interest and inevitable overlap between this, my chosen field, and those with which several of my fellow contributors are to deal.

The remedies which were being administered in 1900 had almost all come into use as the result of empirical observation; their reputation in the majority of cases was based on practical experience and tradition, or even on vague general impression. The purpose of medicinal treatment was then generally held to be that of assuaging the symptoms of disease, leaving a radical cure, if any were possible, to the *vis medicatrix naturae*—how the pompous pedantry of the phrase recalls the atmosphere! "I don't pretend to explain it, but I have seen it do good," was a familiar reply to the student inquisitive concerning the reason for a prescription. The scientifically conscientious physician was frankly and cynically sceptical of the value of any but a few of these traditional remedies. Some of them—mercury, quinine, ipecacuanha—had, by chance, unrecognized actions of the type which we now call "chemotherapeutic" on the specific causes of different infections; others—digitalis, the purgatives, salicylates, morphine, atropine—had established values in the relief of urgent symptoms. Pharmacology concerned itself then chiefly with the finer analysis of the actions of remedies which tradition had thus brought into use; and even on those lines its potential contribution to practice was seldom readily obvious. There was at least some justification for the clinician's familiar gibe—"healthy frogs are not sick men"—as well as for the pharmacologist's lack of interest in a therapeutic practice which used so many drugs of no demonstrable actions for purposes so ill defined.

Already in 1900, however, there were signs from more than one direction of the great change that was on the way. Synthetic chemistry had already begun to intervene, with the production of new artificial remedies, though still on a relatively limited scale. I remember aspirin as a new product, designed to allow salicylic acid to pass through the stomach without risk of its irritating action; aspirin's mild analgesic, hypnotic, and diaphoretic actions were to be discovered later, and by patients, I believe, as much as by their doctors. On the other hand, there were signs already of a much more fundamental change, in the use of a few products of experimental research dealing directly with the causes of disease and not merely with its symptoms. Such were thyroid gland, which Murray had first used in 1891 on the basis of Horsley's experiments, to repair directly the deficiency of the gland in myxoedema and cretinism; and the diphtheria antitoxin, discovered by von Behring in 1891 and made practicable some years later by Ehrlich's more fundamental studies, a direct antagonist to the infective cause of that disease. Both these were established in routine use by 1900, though their direct activity and its scientific basis still gave them a special prominence and an interest of novelty against the generally obscure background of the traditional therapeutics. In 1900, also, Almroth Wright's typhoid vaccine, one of the pioneer preparations of this type, was on trial in the South African War. A discerning student of the literature might, thus early, have detected portents even of the coming of a specific chemotherapy of infections which was to have its effective beginning only a few years later, though the full range of its possibilities would not begin to appear till much more recent years.

I do not think that an adequate impression of the extent and the nature of this change in therapeutics which the fifty years have witnessed can be obtained without examining at somewhat closer range the course and the speed of the developments along each of these different lines. We have to consider the advances made in the immunological and the chemotherapeutic treatments of infections, and in the direct replacement of deficiencies, whether hormonal or

dietary—all these belonging to a type of treatment, essentially the creation of this century, which aims at removing causes; and we must look also at the immense improvement in the range, the effectiveness, and the scientific credentials of remedies applied to relieve symptoms. In no case will it be possible to attempt more than a hasty outline, with details added here and there only by way of example, and not with any idea of presenting a complete picture.

Immunotherapy

The emergence, during the past half-century, of immunology as a practically new branch of medical, biological, and eventually of physico-chemical research and knowledge, with many secondary ramifications and growing-points, is altogether beyond my aim. I can attempt no more than a brief sketch, with many lacunae, of its practical effects on the treatment of infections.

Passive Immunization

As already suggested, it was the practical introduction, just before the turn of the century, of this specific method of treatment, and particularly the use of the diphtheria antitoxin, which started the effective development of immunotherapy. Less directly, it was to play a great part, indeed, in stimulating the search for remedies of other kinds which would also deal directly with the causes in diseases of infection. Diphtheria antitoxin stands to this day as the typical agent of passive immunization, and as still the most important example of its successful use. After its early success it became the principal subject also of experimental studies directed to improving the method of immunizing the animals, mainly horses, used for producing an antitoxin, so as to obtain sera of high natural antitoxic value, and then to concentrate the specific activity into the smallest weight of a globulin, or even of an antitoxic moiety thereof, and therewith into the smallest bulk of solution. The choice of this antitoxin for such researches was largely due to the fact that Paul Ehrlich, in an investigation which will always be one of the classics of immunology, had produced a quantitative method for determining the antitoxic value of any sample in units defined in relation to a stable standard of reference; and this method is still the most accurate of all such biological titrations. Incidentally Ehrlich had thereby effectively laid down the main principles governing all the standardizations by the use of biological tests, which have since provided a basis for the accurate dosage of many different types of the newer remedies. It is perhaps not yet quite certain whether Ehrlich's method of standardizing diphtheria antitoxin gives, by itself, a complete indication of the therapeutic action of the products of the most advanced methods for the concentration and refinement of this serum. There can be no doubt at all, however, that it created the possibility of so early a production of a good antitoxin, and so precise a measurement of its activity, that the first decade of the present century witnessed an impressive revolution in the treatment of diphtheria. From then onwards, in so far as public health administration could ensure the injection of the antitoxin in an adequate dose at the very beginning of the disease, it became possible to reduce the case mortality of diphtheria practically to zero. One of the worst of the spectres which had haunted the minds of parents and of the doctors attending their children up to the end of the nineteenth century had already been laid thus early in the twentieth.

Almost contemporaneous in discovery with diphtheria antitoxin, and second perhaps to it in importance among the agents of passive immunization, was tetanus antitoxin.

It proved to have little, if any, value for the relief of tetanus when once the symptoms had appeared; but its prophylactic value, if administered soon after the infliction of such wounds as were otherwise certain to have produced cases of tetanus, was early placed beyond question. The antitoxin was used in this way, and with very great effect, during the first world war. With it may be mentioned the sera specifically neutralizing the exotoxins produced by other sporing anaerobic bacteria, responsible for gas-gangrene. The immediate availability and use of these sera in the second world war was one factor in the great reduction of a threatening complication of soil-infected wounds; though in this, as in some other directions, immunotherapy was to be supplemented, and later largely to be superseded, by an effective chemotherapy. Curative sera containing antitoxins, or immune substances specifically combining with constituents of bacteria which do not form potent exotoxins, were prepared against the dysentery bacillus of Shiga, and later against a whole range of the antigenically distinct types of pneumococcus. The antidyentery serum had much use in the first world war. In the period between the wars, till after the middle of the 1930's, the use of the type-specific antipneumococcus sera had achieved a dominating role in the radical treatment of pneumococcal pneumonias, especially in the United States of America; though the successive isolation of further types of pneumococcus, each requiring its separate serum, had begun to raise doubts about the eventual limits of such a treatment.

The use of all these specific antibacterial sera, however, was to feel an increasing rivalry from chemotherapy when, in 1935, the extension of this type of treatment to bacterial infections began with the introduction of sulphanilamide and continued with that of its derivatives; and then, before these had yet been fully exploited, came penicillin and the other antibiotics, from 1940 onwards. How far the latter may eventually replace even diphtheria antitoxin is not yet clear. What has become increasingly obvious in recent years is that in dealing with such infections as those of diphtheria or tetanus the therapeutic ideal is not the use either of antitoxins or of antibiotics, to stop the infective process after the latter has begun, but an active prophylactic immunization of the whole population at risk with neutralized or modified forms of the respective toxins.

Active Immunization

The artificial production of an active immunity goes back to Jenner, and was applied in principle by Pasteur. The attempts by Koch, and by others less cautious than he, to produce it with his various types of tuberculin had been so little successful, and in some cases so harmful, that their main effect was probably to discourage for a time any further development along those lines. In any case, when the present century began the more general value of active immunization in human medicine still lacked a practical demonstration on a scale sufficiently large.

Bacterial Vaccines

Wright's typhoid vaccine, consisting of a suspension of the killed bacilli and providing an early example of that type, came just too late for its effectiveness to be fully displayed in the South African War. Before 1914 its value had been established, especially by trials on the Army in India; so that it was then ready to be applied and to produce a brilliant contrast between the almost negligible incidence of enteric fever in the armies of that, the first world war, and the tragic experience in South Africa, where the disease had been more fatal than the Boer bullets. Another vaccine of this type the prophylactic value

of which seems now to have been well established, when the organisms from an antigenically specific culture are suitably prepared, is that of the cholera vibrio. A more general attempt to use, even curatively, vaccines of this kind, made from organisms responsible for a wide range of common and more chronic infections, including tuberculosis, had followed Wright and Douglas's demonstration of a specific "opsonizing" effect of serum from immunized subjects. The use of their "opsonic index" as a quantitative guide to such curative immunization did not find permanent adoption, but it imposed a much-needed restraint on excess in dosage at a time when its introduction had helped to create a wave of enthusiasm and of confidence in the potentialities of vaccines, which later subsided to calmer levels.

Another type of active antibacterial immunization involves the administration of a living culture of a strain of the tubercle bacillus rendered permanently avirulent by a special cultural treatment (B.C.G. of Calmette and Guérin). This has been widely used, first in France and more recently in Scandinavian countries, especially to immunize children of tuberculous parents and nurses and others specially exposed to risk of this infection. Much later than in these other communities, it had just become the subject of systematic trial in this country as the past half-century was drawing to its end; we must wait for the new one to show whether the results will be as favourable here as those reported elsewhere.

Toxins and Toxoids

Remarkable success in the prophylactic production of active immunity has been obtained by the use of the sterile soluble exotoxins of such organisms as those of diphtheria and tetanus, rendered innocuous by neutralizing them almost completely with their corresponding antitoxins or by a chemical treatment converting them into "toxoids," freed from the toxicity but retaining the specific antigenic properties of the toxins. The possibility of such immunization with a nearly neutral mixture of diphtheria toxin and antitoxin was shown by von Behring; but its first practical application on a large scale was due to the vision and advocacy of W. H. Park in New York City, and to Bela Schick's skin test with a small dose of diphtheria toxin, by which evidence could be obtained of the need of the individual for immunization and of its success when applied. Systematic trials by Sheldon Dudley on a controlled community of young naval personnel did much to establish the value of the method in this country. The toxin-antitoxin mixture has been followed by other forms of the immunizing reagent—toxoid (anatoxine of Ramon) produced by treating the toxin with formaldehyde, toxoid-antitoxin mixture, "floccules" specifically precipitated from such a neutral mixture, toxoid precipitated with alum—the list is unlikely yet to be complete. The matter of importance is the complete success of the immunization against diphtheria obtainable with suitably spaced injections of a good preparation of any of the forms of antigen. There are large communities already where the systematic immunization by such methods of all susceptible school-children, with a growing acceptance of general immunization in infancy, has caused the complete disappearance of diphtheria. The experience of the city of Hamilton, Ontario, has often been cited. The incidence of and mortality from diphtheria there had shown for years but minor fluctuations up to 1925, when general immunization was instituted; and both fell then so steeply that in that large population there has been no death from diphtheria since 1930, and no case of the disease since 1933. Other

large cities on the North American continent can now show similar records. The organization and advocacy of such immunization by our own Ministry of Health in recent years have already been followed by a pronounced fall in the death rate from diphtheria, but we shall have no reason to be proud of anything less than the complete elimination from our country of this menace to the life of children.

An equally conspicuous success followed the systematic active immunization against tetanus of armies engaged in the recent world war. A suitable tetanus toxoid was available, and, when an adequate routine of spaced injections had been determined, the effectiveness of the immunization with it was complete. There were, indeed, a few cases of tetanus, and of death in its agony, among those men of the Forces who, yielding to a campaign of persuasion, had refused the protective inoculation. There is a similar campaign now to frighten mothers into refusing, for their children, the protective inoculation against diphtheria. Could any cruelty be worse than these, inflicted by people who believe themselves to be more than commonly humane?

Viruses

Immunization against ultramicroscopic viruses, using strains of modified virulence, had, in effect, been used already by Jenner and by Pasteur. The most successful application of the method in human medicine during the present century, since the existence of such viruses was recognized and their properties brought under full investigation, is probably the immunization against yellow fever, using a strain of the virus transmitted through mice. The solidity of the immunity which follows recovery from many natural virus infections encourages a hope of further successes with artificial immunization in this field. Statistically significant results, though as yet of doubtfully practical value, have been obtained in the large-scale attempts which have been made to immunize communities against the viruses of influenza. Veterinary research and practice appear to have had greater success, so far, with such methods, and it seems likely that more are yet due to be achieved by them in human medicine.

Chemotherapy

Even before the end of the nineteenth century Paul Ehrlich was laying plans to find artificial, synthetic remedies, dealing as directly and specifically with infections by protozoa as the new immunological remedies were dealing with infections by certain bacteria. Quinine, provided by nature, appeared to be such a "chemotherapeutic" remedy for the malarial infection; the project was to discover by artificial synthesis other more potent and less toxic remedies, with an even stronger specific affinity for the infecting parasites and an even weaker one for the organs of the infected host—substances more "parasitotropic" and less "organotropic." Ehrlich had indeed begun this quest with Guttman as early as 1891, when they tried methylene blue as a remedy for malaria; but it was abandoned for the time on account of the impossibility of systematic research, when only occasional cases of malaria, and those in man, were available as subjects for the trial of potential remedies. The real opening of the campaign began with Laveran and Mesnil's discovery that trypanosomes responsible for various animal and human infections in the Tropics could be maintained indefinitely, by serial passage, in rats and mice. Ehrlich seized the opportunity and, with the Japanese bacteriologist Shiga, he had discovered by 1903 a benzidine dye which they named "trypan-red," because of its definite curative action

on these laboratory infections of rodents with trypanosomes. I was myself in Ehrlich's laboratory about the time when this discovery was ready to be made public. It provided the real point of departure for the new scientific adventure of chemotherapy, the development of which, still in vigorous progress, has provided one of the most romantic of all the chapters in the story of this century's achievements in therapeutics.

Dyes and Similar Synthetic Substances

Trypan-red itself did not justify its first experimental promise when it was tried for the treatment of naturally acquired trypanosomiasis in man and the larger animals. Apart from its general and symbolic significance, however, it had a more direct one. It served as the particular starting-point for a series of researches on dyes and substances with comparable structures which culminated, after Ehrlich's death during the first world war, in the discovery, by a team in which his former pupil Roehl was a leading member, of a complex colourless substance named "germanin" by the industrial laboratory in Elberfeld in which it was made, and where its properties were revealed. In this country it has since been made under the name "suramin," and it is probably the best practical remedy yet discovered for the trypanosomal sleeping-sickness of man.

Arsenical Remedies

It will be impossible here to follow in detail the various lines along which chemotherapy has had its effective developments. It must suffice briefly to mention some of the more successful and important. One clue to a new line of advance was provided by the discovery made by Thomas and Breinl, in Liverpool, that the organic derivative of arsenic acid, long known by the trade name "atoxyl," was a more potent remedy for laboratory trypanosomiasis than arsenic in inorganic form. Discovering the true formula of atoxyl, making a more intimate study of the nature of its action, and using further the knowledge acquired in 1905 of syphilis, as due to infection with a spirochaete, Ehrlich and his co-workers arrived by 1909, through many stages, at the arseno-compound which they called "salvarsan." They demonstrated its outstanding activity against spirochaetal infections, and thus for the treatment of syphilis, and chemotherapy therewith attained its first great practical triumph. It would be difficult to exaggerate the effect on medical opinion throughout the world of this first success in producing, by an experimental research organized to that end, a specific remedy, acting directly on a disease of such importance as syphilis, and so rapidly effective that, when it was used at an early stage, an infection hitherto so resistant could be eradicated by a short course of treatment. It would be impossible here to attempt even a sketch of the modifications and improvements which this treatment has undergone; the most recent is the use, in repeated fractional dosage, of the arsenoxide which had formed the last step but one in Ehrlich and Berthelm's synthesis of salvarsan.

An immense stimulus was given by this success to the extension of chemotherapeutic researches in other directions; but for the next quarter of a century the further major successes were relatively few, were practically restricted to the treatment of infections due to protozoa and to spirochaetes, and were thus predominantly concerned with diseases of the Tropics.

As another and later practical outcome of the line of research which, starting from atoxyl, had progressed through arsenophenylglycine to salvarsan (arsphenamine),

mention should be made of trypanamide, the result of researches in the Rockefeller Institute, New York, which seems to have shared, so far, with germanin (suramin) the leading role in the practical chemotherapy of human trypanosomiasis.

Antimalarial Remedies

The Elberfeld laboratories, where methods had first been elaborated for using the malaria-like infections of small birds for preliminary trials, produced two valuable synthetic remedies for human malaria, "plasmochin" ("plasmoquine," pamaquine) in 1926, and "atebrin" (mepacrine) in 1930. The latter was to be successfully exploited by an Anglo-American war effort and to be given its first large-scale trial and systematic investigation when Japan, early in 1942, had seized the world's main sources of quinine; and it was thus to become a factor of very great importance in the fighting strength of the forces by which Japan was ultimately defeated. And meanwhile a co-operative and systematic effort, made also by British and American workers during the war, to find further and better antimalarial remedies had produced several; that contributed by a British team, "paludrine" (proguanil), showing outstanding qualities of low toxicity and efficacy against certain strains, at least, of malarial infection. This availability of effective antimalarial drugs became an important aid, moreover, to new and still actively progressing investigations on the natural history of the malarial infections in man; with the result that the attack on the malaria problem, which even up to the outbreak of the recent war had progressed but little beyond the stage of attempts at mosquito control and quinine distribution, has now at disposal a wealth of new knowledge waiting to be fully exploited, and to produce, it may be hoped, a new and more rapidly progressive phase of this campaign in the new half-century.

Other Protozoal Infections

There are many other examples of the chemotherapy of protozoal infections which would deserve mention for their interest and importance, but I must be content merely to note the successful treatment of *Leishmania* infections, the heavily fatal kala-azar in particular, by organic compounds of antimony and by the purely organic long-chain diamidines.

Chemotherapy of Bacterial Infections

The most remarkable feature, however, of this intermediate period of some twenty-five years was that hardly any success, and none of a practically convincing character, had resulted from many attempts to extend chemotherapy to the ordinary bacterial infections. Ehrlich had encountered an early check in this direction, and the renewed efforts of those who followed him had fared but little better; so that an opinion had come to be held, and seemed to be hardening into a conviction, that, except for certain widely spread spirochaetal infections like syphilis, the prospect for chemotherapy would still be limited to the treatment of protozoal infections and therefore chiefly to that of tropical diseases; while immunology, it seemed, must continue to provide the specific remedies for the bacterial infections predominant in our temperate climate. Then, in 1935 and the years immediately following it, this picture changed completely; the scope of chemotherapy underwent a greater and more rapid expansion than any which had gone before, and with strong reinforcement by a new advance from another direction it continues to this day.

Sulphanilamide and its Derivatives

It was in 1935 that Domagk, of Elberfeld, published his evidence of the effective action of the red dye "prontosil" against streptococcal infections in a number of human cases as well as in experimental mice. Soon there followed the demonstration by Trefouël and his colleagues in the Pasteur Institute, that the much simpler colourless moiety of prontosil, sulphanilamide, was the directly antibacterial agent; and then, in 1936, the first controlled and systematic trial of both prontosil and sulphanilamide, by Colebrook and his team in London, on a series of comparable cases of streptococcal septicaemia. The result put the importance of the discovery beyond question. In 1938 the development of the series of sulphanilamide derivatives began, with Whitby's description of the superior activity of sulphapyridine (Ewins and Phillips) on pneumococcal infections. Clinical trials of this derivative followed, and spread soon to meningococcal and gonococcal infections; and the new order of the success of this treatment was so clear, in all these conditions, that the fame of it began to reach a wider public. Then in rapid succession followed sulphathiazole, sulphaguanidine, sulphadiazine, sulphasuxidine, and the rest—each with its special advantages or its more specific value for certain types of infection. Thus the prospect of sufferers from a whole range of the commoner bacterial infections was transformed in a few years. There were many conditions with which, in default of an effective antiserum, the physician had been restricted to a merely "expectant" treatment or an opportunist attempt to ameliorate symptoms; he now had medicinal weapons to attack the causes of such illness.

Antibiotic Remedies

Long before the possibilities of the sulphanilamide series had been fully developed another chemotherapy of bacterial infections became available, from a quarter widely separated from the synthetic approach envisaged by Ehrlich and so far adopted by his successors. The story has so often been told that it need not be repeated here in detail, of Alexander Fleming's discovery of penicillin through the action of a mould-colony which by accident contaminated a plate culture, and of his partial exploration of its properties in 1929; and then of the new initiative of Florey, Chain, and their co-workers in 1939, which led to its purification and the demonstration of its outstanding practical value as a therapeutic agent, in the first instance for the treatment of infections by staphylococci. The joint achievement, with all that flowed from it, seems certain to rank as one of the main events, with an influence as powerful and far-reaching as any, in the whole history of therapeutic research and its applications. War's urgency had much to do with the rapidity of the development from laboratory experiment to large-scale production; and with the resources thus made available, and an intimate co-operation of leading scientists of the U.S.A. with those of our own country, came the separation of penicillin into several closely related compounds, the determination of the structure of these, and even, in the case of one, the confirmation of that structure by artificial synthesis on a small scale. All these scientific developments, too, were attained with a rapidity which a prognosis based on the standards of peacetime might well have dismissed as incredible.

Penicillin soon proved to have therapeutic applications, first to problems of infection to which war gave special prominence, and then to those of a commoner urgency in peace, far beyond the range of any which would have been predicted. It was soon found to be an effective

remedy for syphilis, as well as for a wide range of bacterial infections. Its actions thus extensively supplemented as well as overlapped those of the sulphanilamide series and even of salvarsan. There were still bacterial infections, however, particularly among those due to Gram-negative and acid-fast bacteria, with which none of these could deal adequately. The filling of these gaps was soon to begin, however, through the rapid exploration of the therapeutic possibilities of a large series of other antibiotic products, to which the brilliant results obtained with penicillin had given so effective a stimulus. What has already been achieved in this direction with streptomycin, "chloromycetin" (chloramphenicol), and aureomycin is matter of a history still in the making. Each of these can claim effective activity against some of the types of infection which had shown resistance to penicillin, as well as to the sulphanilamide derivatives and other chemotherapeutic agents. The evidence that streptomycin will cure tuberculous infection in its acuter and more generalized forms, important in itself and as providing the first clear evidence of the possibility of directly and rapidly eliminating an infection of that kind, opens also a new vista of hope, at least, for the eventual discovery of a similarly effective chemotherapy for the much commoner localized and chronic manifestations of tuberculosis. Chloramphenicol, with its chlorine content and simple structure, which has enabled it already to be produced on a practical scale by synthesis, has among other actions a direct and rapidly curative one on infections due to organisms of the *Rickettsia* group—typhus and related diseases—raising possibilities which till recently had seemed to be almost outside the range of any reasonable ambition. For the rickettsias, obligate parasites with no power apparently of extracellular growth, seem in their dimensions also to be intermediate between the smallest bacteria and the true viruses. With aureomycin the successful treatment of some true viral infections has already been claimed. So that an effective chemotherapy of this range of infectious diseases has come now to be regarded as a likely development, even in the early years, perhaps, of the half-century now beginning.

Replacement of Deficiencies—Hormones and Vitamins

Hormones

The high hopes raised by the treatment of myxoedema with thyroid gland in 1891 that similar successes would be obtained with other ductless glands were to encounter a long disappointment. The isolation of adrenaline (epinephrine) near the beginning of the century had no important bearing on Addison's disease; and the next hormone to be isolated, thyroxine (1915), was concerned with the one endocrine treatment which had already succeeded. The other endocrine extract to be used with success in therapeutics, that of the pituitary posterior lobe, had first been used, like adrenaline, for its symptomatic effects, and not for the repair of any known hormonal deficiency; though its anti-diuretic hormone was eventually to be applied in a true replacement therapy of such a defect in diabetes insipidus. A suspicion had begun to grow, and to strengthen with the passage of some thirty years, that if the other supposedly endocrine glands really produced internal secretions the active constituents of these might be so little stored in the glands, or so unstable, as never to be accessible for direct investigation, or for effective application in treatment. The whole outlook changed in 1921, when the courage, skill, and determination of Banting and Best demonstrated the possibility of separating insulin from the pancreas. This provided another of those landmarks, or points of new

departure, in the field of experimental therapeutics of which we have noted several already; for from that point onwards the atmosphere of therapeutic research on endocrine organs and functions became one of renewed optimism and enterprise. One by one, active preparations from different endocrine glands—parathyroid, suprarenal cortex, gonads, pituitary anterior lobe—were obtained and applied in therapeutics and in further researches. The process of separating the hormones of the anterior pituitary lobe, each acting separately to excite the production or the output of the hormones of another of the endocrine organs, is a matter of special therapeutic interest at present. For one of these anterior pituitary hormones governs the hormonal functions of the suprarenal cortex, including the production and output of the hormone "cortisone"; so that the adreno-corticotrophic pituitary hormone (ACTH) has been used successfully as an alternative to cortisone in that treatment of rheumatoid arthritis which has recently provided a natural focus for so much eager attention. Here again, as the new half-century opens, we seem to be at the beginning of another new chapter in therapeutics, and are wondering what its later paragraphs may contain for us.

Vitamins

The treatment of scurvy with fresh fruit and vegetables seems to have been discovered and rediscovered in each of several earlier centuries, and even the use of cod-liver oil for rickets had long been recommended empirically. The recognition, however, that a natural diet contains small quantities of a number of accessory factors, to which, so inappropriately in the case of many of them, the general name "vitamins" has come to be applied; and the exact knowledge of the diseases of deficiency resulting from the lack of one or other of these in the diet; all these are achievements entirely of the present century.⁴ The paper by the late F. G. Hopkins, from which many would date the beginning of systematic investigations in this field, was not published till 1912. E. Mellanby's investigation producing the first clear evidence that rickets was due to the lack of such a factor in the diet, and that this was a fat-soluble vitamin such as cod-liver oil contains, was published just after the first world war, in 1919. All except the most recent items of the great complex of investigations, by which the vitamins responsible for different aspects of normal growth and metabolism have been chemically isolated and identified, were carried out in the two decades between the two world wars. Till that period, indeed, there had been a tendency to think of the vitamins, like the hormones, as probably present in traces so minute, or as so unstable, that there might never be a reasonable prospect that any would be isolated and chemically characterized. The most recent isolation of a substance belonging to these groups came in 1948, with the practically simultaneous isolation in the U.S.A. and in England of the so-called vitamin B₁₂—the haematopoietic principle of the liver, acting in doses of only a few micrograms to replace the factor missing in pernicious anaemia. It is characterized by the presence of cobalt in its molecule, and might be regarded as either a hormone or a vitamin; and its discovery makes interesting contact with a large body of work on trace elements in the soil and their significance for the growth of vegetation and the health of the stock nourished by it.

Artificial Synthesis

Just as the 1920's may be regarded as the golden decade for the separation of different hormones and vitamins, the 1930's were, in both ranges, that for structural identification

and artificial synthesis. In astonishingly rapid sequence a whole series of hormones, chiefly sterinoid hormones of the gonads and the suprarenal cortex, were thus made artificially from 1930 onwards; Harington's work had led him to the synthesis of the iodine-containing thyroxine already in 1927. From 1930 again, the synthetic production of a series of vitamins with a wide variety of chemical characters came with a like rapidity. In a number of instances the syntheses were applicable on a large scale; so that substances which but ten or fifteen years earlier had still been regarded as doubtfully accessible to any accurate chemical study became now available in quantity for practical use in the prevention or cure of diseases of deficiency, whether hormonal or dietary. The close of the half-century has found expectation keenly alive to the potential significance for therapeutics of an economically practicable synthesis for cortisone, or, perhaps, for the anterior pituitary hormone governing its natural output.

Remedies affecting Symptoms

The past half-century has also witnessed a very great extension of the range and the variety of the remedies available to control or modify symptoms, to ease pain, to induce sleep, and to curb or to stimulate natural activities. These developments have, indeed, a less revolutionary aspect than those discussed in the foregoing sections, in that they have involved no radical change of therapeutic aim from that which predominated in 1900, but mainly an immense increase of efficiency and of recourse to experimental guidance in its practical realization. Apart from opium, morphine, and cocaine, the resources available for analgesia or local anaesthesia were very meagre when the century began: sulphonal was then a standard hypnotic, and the materials available for surgical anaesthesia had changed remarkably little since Simpson introduced chloroform. The barbiturates, basal anaesthetics in general, the range of anaesthetic gases and vapours now available for inhalation, the variety of synthetic substitutes for cocaine and of the methods of applying them—all these are creations of these fifty years. The patient who at first hand can compare the methods of induction and the after-effects of the surgical anaesthesia of thirty, or even of twenty, years ago with those experienced under the best conditions now available will be at least as conscious of the contrast as is the anaesthetist or the surgeon.

It would, of course, be quite impossible to attempt even the most superficial review of changes and innovations in the whole of this vast field. The full enlistment of the powers of synthetic chemistry, and the combination of these with commercial enterprise, have doubtless had the result, in many directions, of producing a redundancy and of presenting therapeutics with a bewildering choice of alternatives. Altogether, however, and in comparison with what was available when the century opened, the result is beyond doubt an enormous enrichment in materials for use in effective treatment, whether these are externally applied, swallowed, inhaled, or given by injection. Overlapping into diagnosis, similar methods have produced a range of substances giving contrast shadows of organs and systems by x-ray photography—a method of which the very basis was a novelty in 1900. Altogether, the main change to be observed in fifty years in the therapeutics dealing with symptoms is the rapid replacement, here also, of empiricism and tradition by methods and remedies based increasingly on the knowledge offered by experimental research. Let me mention but two recent examples of development in that direction, chosen out of a truly immense number available for citation.

Curare and its action have been known since Claude Bernard investigated them a century ago. It is only recently, however, that it has become possible and safe, through a detailed understanding of the method of its action and the means of correcting an excess of this, and through the availability of a pure *d*-tubocurarine, to use it as an adjuvant to surgical anaesthesia giving muscular relaxation; and it has thus become possible to reduce the quantity of the essential anaesthetic to the amount required to secure unconsciousness alone. And now there is news already of at least one synthetic substitute even safer and more effective than any natural curarine; and, since the search began but a few years ago, there are possibilities yet of much further advance.

Experimental evidence, accumulating since 1910, had shown that the symptoms of an allergic reaction are largely due to the action of histamine, released from sensitive cells when the allergen combines with an antibody attached to these. And now there is offered a large and growing series of synthetic substances which can be used to suppress or ameliorate an allergic reaction, by their direct antagonism to the action of histamine.

And these are but examples of a general tendency which in the past half-century, has lifted this treatment of symptoms also to a higher plane of scientific sanction and experimental discovery.

Conclusion

Look back, those who can do so, to the beginning of this century, and recall again the state of medicinal treatment fifty years ago. Heart tonics, purgatives, diaphoretics, analgesics—such, indeed, were in use, and could be reasonably credited with the promotion of a natural function, or the relief of a distressing symptom; but there was a wide range of remedies then still current for which nothing more definite than a generally "tonic" or even "alterative" action could even be suggested. The idea that a remedy could directly remove or neutralize the cause of an illness was still a startling innovation, and neither physician nor patient had yet learned to expect a medication which would go thus to the root of the trouble. Compare such a position with that to-day, when we have become so accustomed to the effective and radical treatment, or prevention, of diseases which till recently were beyond the reach of remedy that there is a tendency to regard the existence of others as a reproach, as well as an incentive, to medical science. Rickets, scurvy, myxoedema, diabetes, pernicious anaemia, syphilis, pneumonia, coccal meningitis, dysentery, typhus—these are no more than a sample from a list which could be made of diseases now brought under such rational and effective treatment that the whole attitude to them, of the public as well as the profession, has been radically changed. It can hardly be doubted that this aspect of medicine, at least, has been the subject of a greater advance since this century began than in all the centuries which went before it. Members of the public who remember the position even thirty years ago, and recognize the contrast between the prospects of sufferers from diabetes, say, or pneumonia, then and now, not unnaturally inquire when anything similarly effective is to be expected for cancer or poliomyelitis or the common cold. The proper reply is surely that, though therapeutics as an experimental science is now on the march, it has only begun to get into its stride. We who have been able to watch the beginning of this great movement may be glad and proud to have lived through such a time, and confident that an even wider and more majestic advance will be seen by those who live on through the fifty years now opening.