foetal structural abnormalities, of presentation and position, of plural pregnancy, of placenta praevia, hydramnios, and the like, as well as giving us methods of accurate assessment of the mother's pelvic capacity.

In this brief survey of the progress of midwifery I have had to avoid some attractive digressions into gynaecology, haematology (Rh factor), cardiology, foetal pathology (rubella in early pregnancy), and paediatrics. I have omitted any reference to the training of the medical student in midwifery, because it is too wide a topic, and to the training and control of midwives, because that falls under "Legislation." But there is one last achievement which must be mentioned, since it is not merely a milestone but a monument to the progress of obstetrics and gynaecology.

The Royal College of Obstetricians and Gynaecologists

In 1928 the British College of Obstetricians and Gynaecologists was founded, with William Blair Bell as its first president and William Fletcher Shaw as its first secretary. Broadly and briefly speaking, the establishment of the College was the natural and evolutionary outcome of the maturity of obstetrics and gynaecology as a conjoined branch of medicine. It signaled the blossoming of the branch, and we are now beginning to see the beneficial fruiting. The phenomenal success of the College in its first twenty-one years has been the best proof of how much it was needed in the interests of the two subjects not only in Britain but throughout the whole British Commonwealth. It has been singularly helped by royal favour, not only in the grant of a royal title and charter but in the active and generous personal interest of Her Majesty the Queen, who is an Honorary Fellow as well as Patron. Better proof of the "maternity-mindedness" of this generation could not be offered.

FIFTY YEARS OF MEDICAL RESEARCH AND PRACTICE

BY

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"The art of progress is to preserve order amid change, and to preserve change amid order."—
A. N. WHITEHEAD in *Process and Reality*.

"The last fifty years!" The phrase slips glibly off the tongue. Yet no era in the world's history has been so crowded with events of greater import for man or medicine. The twentieth century opened with Victoria still on the throne, and four monarchs were to succeed her. The conflict still raged in South Africa, and two wars were to follow and embroil the whole world. Each war was to overshadow its predecessor in ferocity, cruelty, tragedy, and destruction, until in the last it seemed that civilization itself might perish. Yet "out of evil came forth good," and medicine was enriched through the envies, bitterness, and follies of mankind. The third Marquess of Salisbury was Prime Minister; to-day his grandson is a notable figure in the House of Lords. The first underground electrical railway—the Central—opened in London in 1900; the first motor-bus and aeroplane, the first cinema and radio programme, and a host of other amenities and amusements without which it is to-day almost impossible for the vast majority of mankind to contemplate an acceptable life were still

unknown. And legislation was to change, for good or evil, the social structure in every country in the world.

It is in this background and perspective that we must view the advances in medical knowledge and practice in the same period, for the history of medicine reflects the philosophy of its time. The dramatic discoveries in the basic sciences during this period gave to medicine its most potent instruments of research and tended to place the focus of medical advance in the laboratory rather than at the bedside, but the older methods which had their roots in the nineteenth century and even earlier were still to yield a rich harvest. For advance in knowledge is essentially evolutionary, not episodic; and no advance in clinical research leaves uninfluenced for long the practice of medicine.

Methods of Clinical Research

The methods by which clinical research and practice have progressed defy clear-cut enunciation. Few discoveries reach maturity without all known methods being employed, but in most can be discerned the motivating and predominant role of one of four methods. First, the recognition of clinical syndromes or recurring patterns of disease, commonly called "entities" or "diseases," and their investigation by all available techniques—pathological, biochemical, radiological, epidemiological, statistical, etc. When new techniques are developed they can be applied to earlier established syndromes and new knowledge gained. For example, the development of bacteriological techniques and their application led to the aetiology of many infectious diseases being revealed.

Secondly, experimental laboratory research has pointed the way to the interpretation of known clinical syndromes; from this, for example, we learnt to associate diabetes mellitus with the pancreas and diabetes insipidus with the hypothalamus.

Thirdly, there is the chance observation; the story of penicillin illustrates vividly the fact that though good fortune may attend discovery it comes only to the mind prepared for it.

And fourthly, there are the major discoveries in the cognate sciences—physics, chemistry, biology, psychology, and sociology—applied to the investigation of health and disease in the hope that these may yield some of their secrets.

It is of interest to trace in a few of the major advances in medicine in the last half-century the part played by these various methods, and the importance of perspicacious planning, a clear objective, concentrated effort, and team-work to clinical research.

Endocrinology

In few fields can the influence of these principles be better exemplified than in those of endocrinology and nutrition. Graves's disease, Addison's disease, myxoedema, and acromegaly had been described and their morbid anatomy was known before the century opened; and experimental excision of the adrenals had been shown to produce a fatal syndrome analogous to Addison's disease, and pancreatectomy a fatal glycosuria. But the science of endocrinology as we know it to-day is virtually a product of this century and begins with the discovery by Bayliss and Starling in 1902 of secretin, the first of the "hormones," or chemical messengers, which exerted a humoral as contrasted with a nervous control in the body. It was soon recognized by clinical observation and its correlation with pathological findings, by observing the effects of excision of glands both in the experimental animal and, in

rare instances, by operations on man, and by injection of their extracts or grafting transplants, that the pituitary, thyroid, parathyroids, suprarenals, pancreatic islet tissue, and gonads exercised a profound influence on such functions as growth and metabolism; whereas no hormonal function could with certainty be attributed to the pineal or the thymus, although thymectomy exerted a beneficial effect in many cases of myasthenia gravis.

But what is perhaps of greatest importance is that, during this century, study of the endocrines has led to a different orientation of medicine itself. The stress has shifted from alterations in structure in terms of morbid anatomy to disturbances of function in terms of morbid physiology. Since such disturbances could be in one of two directions—either excess or defect—clinicians sought to detect syndromes which could be interpreted in these terms. Thus tetany came to be recognized as an expression of parathyroid defect, and generalized osteitis fibrosa cystica one of parathyroid excess; the hyperglycaemia due to pancreatic islet deficiency was found to have its counterpart in hypoglycaemia due to overactivity of the islets. Where more than one type of cell entered into the composition of a gland, clinical research revealed syndromes associated with each type. The virilism of a suprarenal cortical adenoma was in striking contrast to the paroxysmal hypertension of the medullary chromaffinoma. The Cushing's syndrome of a pituitary basophil adenoma showed no superficial relationship to the gigantism and acromegaly of eosinophil overgrowth.

Indeed, we are to-day able readily to recognize most of the syndromes associated with excessive or defective secretion of the many endocrine glands and the various cells which comprise them; and where they are not yet recognizable we can prophesy, with the same confidence that the filling of gaps in the table of atomic numbers was foreseen, that sooner or later they will reveal themselves in the clinic.

The morbid anatomy of excessive activity of a gland may be a diffuse hyperplasia or hypertrophy, though more commonly a neoplasm, simple or malignant, is found arising from one type of cell, hence the specificity of the clinical pictures even in compound glands. But failure of growth or maldevelopment, and such destructive processes as inflammation, injury, degeneration, ischaemia, invading neoplasms, and the like, tend to destroy the whole gland. Hence, for example, although we recognize different syndromes related to neoplasms of the eosinophil and basophil cells of the pituitary, there is only one known syndrome of pituitary destruction—Simmonds's syndrome in the adult, and Lorain's syndrome in the child.

Thus during this century the concept of "diseases" as of "certain and determinate kinds" possessing "certain distinguishing signs which Nature has particularly affixed to every species" (Sydenham) has given way to the percept of "disease" as a disorder of function, accompanied by related structural changes, and brought about by many agencies, some necessary and specific, others predisposing, precipitating, and perpetuating.

The past fifty years in medicine has been marked by an increasing application of physico-chemical methods to the elucidation of disturbances of function in disease. For example, during the first twenty years of the century micro-methods of blood analysis were perfected, and were applied, amongst others, to the study of endocrine disorders. Results of far-reaching significance in both diagnosis and treatment ensued. The disturbances in salt and water metabolism in Addison's disease and the place of salt in its treatment may

be noted as a direct outcome of these studies, and it is doubtful if insulin or the parathyroid hormone would have been isolated if no method had been available for the estimation of the glucose or calcium of the blood.

The dramatic benefit which Murray had brought to the victims of myxoedema in 1891 by feeding them on extracts of sheep's thyroid—his article was published in the *British Medical Journal*—and the appreciation of the importance of hormones in the early part of this century, led to attempts to isolate other active extracts. Adrenaline in 1895, oxytocic pituitary extracts in 1909, the growth hormone of the anterior pituitary and insulin in 1921, oestrin and the gonadotropic hormone of the anterior pituitary in 1928, and the adrenal cortical hormone in 1929 are examples which not only filled a place in therapeutics as replacement remedies but were found to have other beneficial actions—e.g., adrenaline in asthma and pituitary extract in diabetes insipidus.

But these were relatively crude extracts, which provided a fertile field of action for the pure organic chemist. From many of these extracts were obtained pure crystals of biologically active substances. On Christmas Day, 1914, Kendall isolated in crystalline form the thyroid hormone, thyroxine, so potent that it was estimated that $3\frac{1}{2}$ gr. (0.23 g.) was the body's yearly requirement; in 1925 crystalline insulin was obtained, and in 1934 and later Kendall isolated a large number of crystalline hormones from the suprarenal cortex, all of similar structure, which included not only desoxycorticosterone acetate ("doca"), which plays an important though not exclusive part in the therapy of Addison's disease, but also "cortisone" or "compound E," which promises to revolutionize our treatment of arthritis and our understanding of the metabolism of connective tissue and immunity reactions.

The next stage was the determination of the constitution of these crystals and their laboratory synthesis. The structural formula for adrenaline was early revealed, but, although Kendall had isolated thyroxine in 1914, it was eleven years later that Harington showed it to be a derivative of tyrosine and assigned to it its proper structure, and a year after this that Barger synthesized it. As yet many hormones, including insulin, have defied synthesis, possibly because they have a protein structure, but some of the most complex have yielded their mystery to the skill and ingenuity of the organic chemist. And he has gone even further. It has been held, and there is much to support the view, that "Nature is still a cleverer chemist than man." Recent discoveries throw doubt on this assertion. Natural adrenaline is ineffective when given by mouth; the chemist has produced a synthetic adrenaline—isopropyl-nor-adrenaline—which is most potent orally. The natural oestrogens are complex cyclopenteno-phenanthrene derivatives and are of little effect when given by mouth. Dodds and others have synthesized artificial oestrogens of quite different and much simpler chemical configuration (alkylated derivatives of dihydroxystilbene). The general biological action of these is identical with the natural oestrogens, but they are active by mouth, can be of much greater potency with a more prolonged action, and are more cheaply prepared. The twentieth-century organic chemist may not have improved on Nature, but he knows a trick or two which are hidden from her.

There is a related study of which the last twenty-five years have revealed only the fringes, yet it may well be one of the most significant and rewarding in the years immediately ahead. It arises from three facts. First, that adrenal cortical hormones, including corticosterone and

compound E, the natural male and female hormones (androgens, oestrogens, and those of the corpus luteum), and methyl cholanthrene—a potent artificial carcinogen—have all as their characteristic ring system cyclopentenophenanthrene. Secondly, that oestrogens markedly inhibit the spread and growth of prostatic carcinoma, and to a less extent both oestrogens and androgens influence favourably the metastases of breast cancer. And thirdly, that cortisone seems to play an important part in the immunity reactions of the body. Are these three facts significantly related or is their association fortuitous? If the former, the solution of the problem of cancer and its control may be in sight.

Nutrition

Although the consequences of starvation and of fluid and salt restriction have long been recognized, and such syndromes as rickets, scurvy, beriberi, and pellagra known for centuries and associated with deficiency states, this century's contribution to research in human nutritional disorders has revolutionized our knowledge and transformed our practice. In this the study of vitamins and the part played by essential amino-acids are outstanding.

In 1885 Takaki showed conclusively the dietary origin of beriberi, and the measures he introduced led to its eradication from the Japanese Navy, where earlier it had been a serious problem. Over a century had then passed since Lind, by urging the issue of lemon juice, had performed a similar service which was to lead to the disappearance of scurvy from the British Navy. The early twenties of this century saw from Mellanby the first convincing evidence that rickets is a deficiency disease curable by a correct diet, and that the prevention of pellagra is through a proper diet.

The laboratory studies which were to reach fruition in this century began with Lunin's observation in 1881 that animals cannot live on a synthetic milk diet. In the last decade of the nineteenth century Eijkman had produced beriberi experimentally in fowls, the first time that a disease of dietary deficiency had been so produced, and he established that a diet of overmilled rice was the chief cause of beriberi.

But it was from Gowland Hopkins and his school that the major contributions were first to come, and within a few years there followed the isolation of individual vitamins, the recognition of the clinical and experimental lesions to which their deficiencies gave rise and of their modes of action, the determination of their chemical structures, and their large-scale manufacture. We now have the medical knowledge which, if applied, could virtually eliminate nutritional disorders. The planned rationing of the second world war, contrasted with the effects on the nutrition of the combatant nations of the first, is ample confirmation of this assertion. In the field of nutrition medical scientists have accomplished in great measure the tasks which confronted them. The next step lies with statesmen.

Haematology and Vitamin B₁₂

There is one chapter in the story of medical research which may profitably be summarized here, not only for its intrinsic importance but because it illustrates so strikingly the methods of clinical research in the past fifty years and the contributions made to it by workers in diverse scientific fields, each pursuing knowledge for its own sake.

Haematology has during this century been enriched by studies on the development of blood cells and their morphology, by the examination of haemopoietic tissues during life by marrow biopsy, by methods of blood chemistry and

determinations of the physical properties of blood, by the application to the study of blood disease of genetics and immunology, and in a host of other ways. New clinical syndromes have been described, such as the anaemias associated with the names of Cooley and Lederer, and the Plummer-Vinson syndrome. Chlorosis, of which a lucid description had been given by Hoffmann over two centuries ago, and which was, to judge by the literature, a common disorder early in this century, was gradually to die out as the years advanced. The anaemias associated with iron deficiency were more clearly defined, and the need for adequate dosage of iron in their treatment was demonstrated. When the century opened the fifty-year-old problem of the essential nature and effective treatment of Addisonian (pernicious) anaemia remained unsolved. As the years passed it was increasingly recognized that it was not a disorder of blood-forming tissues only, but that the nervous and digestive systems were commonly affected. The neuropathies involved the peripheral nerves, the spinal cord, the optic nerves, and the cerebrum; glossitis and achlorhydria were signs of alimentary changes. Until twenty-five years ago treatment was confined to such measures as giving arsenic, hydrochloric acid, and blood transfusions, but life was rarely prolonged for more than a few years.

In 1925 Robscheit-Robbins and Whipple showed the beneficial effect of raw beef liver on blood regeneration in anaemia, and a year later followed the demonstration by Minot and Murphy of the specific effect of liver in pernicious anaemia. In 1929 Castle found that from the gastric mucosa could be obtained a substance active in the treatment of pernicious anaemia. Then came years of intensive research into the nature of the essential factor in liver. Although extracts of such potency that a few milligrams each month were adequate to maintain the patient with pernicious anaemia in good health, the pure active principle eluded isolation. Two facts contributed to this failure. The first was the difficulty of manipulating very small amounts of material for the processes of chemical separation; the second, the absence of a simple and rapid test for the haemopoietic activity of the isolated substances. The only subject for such a test was at that time the victim of the disease. The solution to both problems was to be culled from unexpected sources—the first from organic chemistry, the second from bacteriology.

The organic chemist in his investigations, especially on the isolation of plant pigments, had shown that when a mixture of these was passed down a specially prepared cylindrical filter, rings appeared at different levels at which the various constituents separated out ("partition chromatography"). Each of these rings could be removed and its content extracted. This made the separation of the different constituents of the liver extract a much simpler process. The bacteriologist had found that folic acid (one of the components of the vitamin-B complex) was an essential growth factor for *Lactobacillus lactis* (Dorner). Folic acid is an efficient haemopoietic agent in macrocytic anaemias though not an effective substitute for liver in pernicious anaemia; it fails to protect against the neural dystrophies in this disease. But it was shown that the anti-anaemic potency of liver extracts runs parallel to the growth requirements of the lactobacillus. This gave a simple and accurate method of rapid laboratory assay. By the application of these two discoveries in widely separated fields of science the isolation of vitamin B₁₂ was made possible.

No topic could more vividly illustrate the lesson of the first half of this century that knowledge is an interlacing

network and that strands from many sources intermingle to give it fullness and strength.

Cardiology

The topics so far discussed have shown us a few of the notable contributions which during this century the chemist and biochemist have made to clinical research, and consequently to the practice of medicine. But the part played by the physicist has been no less noteworthy. Radio-diagnosis and radiotherapy, the construction of instruments designed to record the minute change in electrical potential accompanying activity in muscle, both voluntary and cardiac, brain, nerve, and even the retina, have led to results of great significance in our understanding of disease and in clinical diagnosis. All branches of medicine owe a debt to physics, but as an illustration of its contribution a brief survey of the evolution of our knowledge of heart disease during the present century is apt. A glance at the fourth edition of Osler's *Principles and Practice of Medicine* (1901), the most popular textbook of its day, suffices to reveal how little was then known. Most of the irregularities of the heart's rhythm remained undifferentiated and their significance was a sealed book.

Early in the century Mackenzie used in his general practice in Burnley a simple instrument, the polygraph, which recorded simultaneously the cardiac, venous, and arterial pulses. His genius enabled him by an analysis of these records to recognize the nature of most of the cardiac irregularities with which we are to-day so familiar; and long observation of patients led him to assess their significance and to differentiate those which could be ignored from those of grave import.

At the outset of the century Einthoven was perfecting the string galvanometer and was to show in 1903-4 how it could be applied to recording the electrical changes occurring in the human heart. In Lewis's hands this instrument was to reveal the mechanism of the heart beat and its disturbances in disease. Through him it was to become a diagnostic weapon without which no clinic was complete. In its development and use it was destined not only to illuminate disturbances of rhythm and conduction but also to throw light on the site and extent of coronary disease—one of the gathering enemies of mankind. Soon after, methods for recording the sounds of the heart and relating them to the electrocardiogram were devised.

What is sometimes forgotten, though it is of the utmost importance to the practice of medicine, is that the analysis and differentiation of, for example, the disturbances of rhythm revealed by these instrumental methods prompted the clinician to return to his patient and try to discover why the nature and import of these had earlier escaped him, and whether, with the additional knowledge gained through the instrument, he could now recognize by his own unaided observation what the instrument had revealed. He soon found that he was able to do so, and that he seldom needed the instrument to recognize extrasystoles and their type, auricular fibrillation, heart block, and the like, though in the difficult case instrumental help was still indispensable. With improvements in the techniques of physics other means of recording the electrical changes of heart and nerve have been introduced—e.g., the cathode-ray oscillograph.

The application of radiology to heart lesions revealed to the physician the pitfalls of his arts of percussion and auscultation, on which he had earlier relied. It made possible the recognition during life of such lesions as cardiac aneurysms. The injection of radio-opaque materials into

the blood stream and observing the direction of flow and admixture of blood in the chambers of the heart (angiocardiology) have often made radiology the final arbiter in deciding, for example, the nature of a congenital cardiac lesion and its suitability for surgical repair.

As the years have passed, chemistry, especially the analysis of blood gases, has come to play an important part in the investigation of the problems of heart disease. Under radiological control, catheters can be passed through peripheral veins into the different cavities of the heart. The taking of samples of blood from these has helped to assess therapeutic measures in circulatory failure and to establish diagnosis, especially in malformations. These tests have often proved a necessary prelude to successful surgical intervention. The increasing contribution of surgery to the treatment of such lesions as patent ductus arteriosus and coarctation of the aorta demands accurate diagnosis. Surgery of the heart and lungs has been aided also by advances in antibiotic therapy, improvements in anaesthesia, and in measures for combating shock and blood loss. Investigations which have for their object the maintenance of an efficient cerebral circulation whilst the heart being operated upon is isolated from the circulatory mechanism are reaching a stage at which success seems in sight.

The introduction by Riva-Rocci of the mercury sphygmomanometer in 1896 led during the ensuing years to increasing interest in the significance and mechanism of high blood pressure. Few clinical problems have been so extensively investigated in the past fifty years, but, though much light has been shed on certain forms of hypertension by laboratory and bedside studies, knowledge of its intrinsic nature and its effective management still remains meagre.

The application of physical instruments of great precision has not been confined to cardiological practice. The electroencephalograph, following on Berger's discovery in 1929 that action currents of brain activity can be registered, has opened new fields of investigation in the epilepsies and in the localization of cerebral lesions, and the electromyograph is helping increasingly in the diagnosis of muscular lesions. Moreover, improvements in lenses and in lighting have led to the devising of instruments which make it possible to see into the cavities of the body. The sigmoidoscope, cystoscope, oesophagoscope, gastroscope, bronchoscope, the electrical ophthalmoscope and laryngoscope, and many other ingenious instruments have been constructed, and cameras for permanent recording attached. The electron microscope has opened new fields of research into the ultramicroscopic world, especially of viruses.

Radioactivity

The immense significance to medicine of Röntgen's discovery of x rays in 1895 was immediately recognized, and within a year or two it was applied to the diagnosis of bone disease and injury, stones in the urinary tract, foreign bodies, and similar lesions. With improvements in technique the softer tissues—e.g., the lungs and kidneys—were later visualized in sufficient detail to be of considerable help in diagnosis, and as the years have passed in this century the ingenious use of contrast media—e.g., barium in the alimentary tract, lipiodol in the bronchi and spinal theca, air in the cranium and peritoneum, iodine derivatives in genito-urinary and biliary tracts, the circulation, etc.—have made x-ray examination an almost indispensable contribution to accurate diagnosis in innumerable diseases.

Becquerel's chance observation of the destructive effects of radium, which the Curies had isolated in 1898, although

following the earliest use of x rays in treatment, was the starting-point of the science of radiotherapy, which has seen such strides in the past few decades.

But what could not have been foreseen was the gift to medical research which fundamental investigations into the structure of the atom was later to yield through the genius of Thomson, Rutherford, and their co-workers, especially Chadwick and Aston. In 1934 came the outstanding discovery of Curie and Joliot, that ordinary elements which are found in nature in the stable state can be induced to become radioactive. Investigators thus had at their disposal atoms of a wide variety of elements of biological interest, which by means of special recording instruments could be easily traced by their radioactivity. Thus a method became available for following "labelled" atoms in the myriads of complicated reactions which occur in the body, both in health and in disease, and also for delivering radiation treatment direct through the blood stream to the various tissues of the body. A few examples will suffice to illustrate the uses to which these radioactive isotopes have been applied.

Radioactive iodine (I^{131}) has been used in studying the physiology of the thyroid, in the recognition of thyroid disease, in the location of brain tumours with diiodo-fluorescein, and in the treatment of hyperthyroidism and thyroid carcinoma. Radioactive phosphorus (P^{32}) has found a special place in the study and treatment of blood dyscrasias—polycythaemia, leukaemia, lymphosarcoma, and myeloma; in metabolic investigations on nucleo-proteins and phospho-lipoid synthesis; in the elucidation of the malaria-plasmodium-host relationship; on the vascular capacity of heart and kidney; and on the fate of labelled antigens and rate of antibody production. Radioactive calcium (Ca^{45}) has made significant contributions to our knowledge of bone growth, and radioactive sulphur (S^{35}) to the role of sulphur-containing amino-acids in protein metabolism. The life story of the red blood cell has been illuminated by radioactive iron (Fe^{59}), and a wide variety of uses in medical research are being made of radioactive carbon (C^{14}), sodium (Na^{24}), potassium (K^{42}), and other elements. This is yet an infant field, but few infants have shown greater promise of vigorous growth.

Infectious Diseases and Allergy

The last three decades of the nineteenth century had seen rapid strides in our knowledge of the infective agents in disease. Among bacteria had been described staphylococci, streptococci, pneumococci, meningococci, and gonococci; the bacilli of typhoid, tubercle, leprosy, glanders, tetanus, undulant fever, diphtheria, plague, dysentery, and gas gangrene; the malaria parasite and the entamoeba of dysentery; and fungi of actinomycosis and sporotrichosis. The role of vectors, especially in tropical diseases, was well established. The first twenty years of the twentieth century saw an intensive development of bacteriology and protozoology and the recognition, using special media and techniques, of tens of thousands of organisms of which only a small proportion could be regarded as responsible for disease. Many new diseases, including tularaemia, histoplasmosis, toxoplasmosis, melioidosis, and others were recognized.

The phenomenon of bacterial agglutination, discovered in 1896, had been rapidly followed by its application to the diagnosis of typhoid, and later to dysentery, brucellosis, and other infections. Clinical pictures superficially similar, as, for example, the enteric fevers, were found to be due to organisms which differed in their cultural characteristics,

their fermentative properties, and their agglutinins. The many types of paratyphoid, dysentery, and food-poisoning infections were differentiated. In 1901 the phenomenon of complement-fixation had been discovered, and five years later, and just one year after the *Treponema pallidum* had been revealed as the causative organism of syphilis, came the Wassermann reaction. Later the complement-fixation test was applied to other diseases. Vaccines, antisera, and antitoxins were soon to follow, and then came prophylactic immunization in diphtheria and whooping-cough, which was to have so great an effect on infant mortality from these diseases and to give promise of similar success in tuberculosis by the B.C.G. vaccine.

The production of antibodies in the blood of infected patients, however, was not only to lead to these mighty therapeutic advances but was also to throw light on a group of diseases of which but little was earlier known. Before 1890 there were scattered observations in the literature suggesting that certain cases of asthma were caused by the inhalation of dusts, pollens, and dandruff, that urticaria and "gout" occasionally resulted from an idiosyncrasy to food, and that eczema might follow on contact with certain plants. But it was the reactions from diphtheria antitoxin—serum shock, serum disease, and anaphylaxis—that led to the conception of allergy as a tissue sensitization, inherent or acquired. This was to have an important influence on the interpretation of disease in this century. Advances in these directions have almost transformed the taxonomic bacteriologist of the earlier part of the century into the immunochemist of to-day, and advances in chemotherapy have revolutionized, as Sir Henry Dale so vividly relates, the treatment of infectious disease.

Many diseases were from their clinical characteristics suspected of having a bacterial origin, yet the methods in use failed to reveal it. This century has seen the isolation and significance of two further groups of pathogenic organisms—the rickettsiae and the viruses. The rickettsiae are minute bacteria causing, for example, typhus, but they are of little interest in this country. It is just fifty years since a virus was established as the infectious agent of tobacco mosaic disease; in a decade or two, yellow fever, rabies, vaccinia, variola, and poliomyelitis were identified as of virus origin; and to-day, with similar methods of isolation being used, there is reason to suspect that herpes zoster and febrilis, varicella, psittacosis, influenza, many forms of encephalitis, warts, and molluscum contagiosum, amongst other infections, are due to viruses.

In the earlier part of the century we see in retrospect an undue emphasis on the role of living organisms in the causation of disease. This was an understandable response to the isolation of a specific cause and the rigid application of Occam's razor—"Entities should not be multiplied beyond necessity." But as the years passed it came to be recognized more widely that the organism, though a necessary agent, is rarely sufficient of itself to produce disease; that constitutional bias, the nutritional state, occupation, exposure, and a host of physical and chemical factors play a part in all infections; and that the manifestations of the disease are modified by all these factors. It is indeed the appreciation of these predisposing and perpetuating causes of disease that has led in the past twenty years to the emergence of "social medicine" as a separate discipline.

Neurology

The help given to neurological research and diagnosis by radiology, especially pneumoencephalography and arteriography, and by electrophysiology has been earlier

acknowledged. It is in this province also that clinico-pathological correlation, the main instrument of medical research in the late eighteenth and nineteenth centuries, has continued in this century to make valuable contributions. The recognition of many new syndromes—e.g., Wilson's disease—has thrown light on the functions of the basal ganglia and the related subthalamic nuclei, and to this study the epidemic of encephalitis and its after-effects from 1917 onwards gave fresh impetus. The first world war provided the opportunities which led to the classical work by Gordon Holmes on injuries to the visual cortex and cerebellum and, with Head, on sensory pathways and aphasia. Sherrington's fundamental work in neurophysiology, especially on reflexes, tonus, and integrative mechanisms in the nervous system, was to find important applications in neurological practice. Many new reflexes were to be described on the basis of necropsy findings—e.g., the extensor plantar response in pyramidal disease. The work of Golgi and Ramón y Cajal on neurohistology was to be extended: one of its fruits was the monograph by Bailey and Cushing on gliomas—a classical example of the fertile collaboration of clinician and pathologist.

In the past thirty years the neurosurgeon has been able to add to our knowledge, especially on cerebral localization and epilepsy, by direct observations, on man, of the effects of stimulation of the exposed brain.

In this context it is proper to refer to the growing recognition of the part played by psychogenic factors in disease associated with structural change—e.g., in peptic ulcer and allergic states. In recent years this has led to a concept of psychosomatic medicine which has re-emphasized the absurdity of body-mind dichotomy.

Conclusion

The tests which have been devised to assess the functional efficiency of most of the organs and tissues of the body and the use made of these in diagnosis and in the control of treatment; the major advances in therapy, both medical and surgical, especially in recent years; the achievements of preventive medicine; and many other topics which are the subjects of separate contributions to this symposium testify to advances in practically every branch of medicine no less serviceable to mankind than those here reviewed.

But the story must not be thought of as one of unimpeded and triumphal progress nor narrated wholly in the jubilant terms of victory. For the mastery of many diseases still evades our grasp and most conquests have brought forth fresh problems. The treatment of cancer is still based on a primitive and barbaric interpretation of the injunction, "If thy right hand offend thee cut it off," though recent years have given hints of deeper understanding. The expectation of life has risen in the past half-century by about fifteen years. Yet increasing longevity has its hazards in the greater incidence of cancer and degenerative disease of the heart, blood vessels, and brain.

The obstacles to be surmounted in the control of disease are still many, but, with the experience of the first half of the twentieth century in mind, he would be a bold prophet who would venture to predict the limits of future achievement. More heights will be scaled, and on their summits may be firmly planted the emblems of progress; but some will reveal that the topmost heights are not yet reached. To conquer these, wisdom will bid us recall the one lesson above all others which the story of "combined operations" here related teaches—namely, that every branch of knowledge has its contribution to make to the goal of medicine, and that this goal is not only the prevention and cure of

disease but also the raising of standards of individual and community health, taking as its motto the words of Martial: *Non est vivere, sed valere vita est*—Life is not living, but living in health.

FIFTY YEARS OF CLINICAL PATHOLOGY

BY

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The title of this article naturally raises the question of what is meant by clinical pathology. When does pathology become clinical, as distinct from an academic pure science several stages removed from everyday medicine, and when does clinical work become inseparably associated with procedures which can be performed only in a laboratory, rather than at the bedside? One might define clinical work in simple terms as that work which can be performed at the bedside. But it is impossible to separate this work from pathology, in that the clinician is observing and pronouncing his opinion upon pathological processes many of which are susceptible of laboratory investigation and control. The evolution of clinical medicine was gradual, whilst the impingement of the laboratory upon the bedside has become ever more prominent in the past fifty years in parallel with the geometrically progressive speed of scientific advance.

At the close of the nineteenth century the practice of clinical medicine had reached a remarkably high standard. Those were the days of the great individualist, of the outstanding man who, with no more equipment than his five senses, his experience, a few crude instruments and rough side-room tests, his wits and his instinct, would make a shrewd and remarkably accurate assessment for prognosis and diagnosis, though treatment was limited by lack of knowledge of primary cause or of specific measures. There were no exact checks upon the accuracy of the opinion apart from the final assessment in the post-mortem room. Be it said to their credit that most clinicians of the period, though opinionated and dogmatic at the bedside, more often than not with full justification, nevertheless regularly checked their opinion in the post-mortem room, thereby deriving experience and knowledge from their mistakes. They frequently performed the post-mortem examinations themselves, and usually conducted lectures and taught the pathology and morbid anatomy of disease—work which nowadays is carried out by a department of pathology.

These masters of the bedside art combined their clinical work with the practical pathology of their hospitals; they were well versed in morbid anatomy and in the limited tests for physiological functions which were then known. Their views, their teachings, their wisdom, and their technique spilled over into the twentieth century, so that many whose age is parallel with or in advance of the years of the century are greatly indebted to them for a clinical teaching the excellence of which is never likely to be seen again. Nowadays the tempo of life is so fast, the demand for medical treatment so large, the detail of every specialty so great, and the complexity of scientific checks and treatment so vast that no one man could achieve such general excellence and with such unhurried or courtly confidence as the masters of the past.

Meanwhile, behind the foreground of the clinical perfection of the nineteenth century the science of pathology,