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

Sir LIONEL WHITBY, C.V.O., M.C., M.D.
F.R.C.P.

Regius Professor of Physic, University of Cambridge

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,

which included bacteriology, immunology, histology, morbid anatomy, and the early phases of haematology and chemical pathology, grew apace and began to extend into clinical medicine by reason of practical applications.

Bacteriology

Pasteur, Koch, and others had established the bacterial nature of many diseases. Hence it was often possible to prove a causal factor by successful demonstration of the specific organism in smear or culture of appropriate material. Immunological studies had established the specificity of antibodies and had shown the virtues of at least one specific antitoxic serum—for diphtheria. Hence a bacteriological check could confirm the necessity for diphtheria antitoxin or could go some way towards identifying the likely candidates for antitoxin treatment before clinical signs had appeared. Furthermore, certain of the phenomena associated with immunity—agglutination, precipitation—were seen to be applicable to the diagnosis of active disease. Grüber and Durham in 1896 had shown that the serum of patients suffering from typhoid fever would agglutinate the typhoid bacilli, while Widal and Sicard in the same year extended the discovery to show that a patient's serum could be tested with bacteria of known type for the purpose of identifying disease. This principle, which is often called Widal's reaction, should rightly be called the Grüber-Widal reaction.

Bacteriology and immunology were in fact the first of the laboratory sciences to make any considerable intrusion into bedside medicine, and in the early phases these sciences demanded no more than an appropriate sample of a body fluid, a secretion or an excretion, which could be competently examined. For example, in 1901 Bordet and Gengou had established the principles of the complement-fixation reaction, which Wassermann, Neisser, and Bruck extended in 1906 as a specific test for syphilis soon after Schaudinn and Hoffmann in 1905 had demonstrated the spirochaete and Levaditi (1906) had stained it. In 1904 Almroth Wright and Stewart Douglas announced their work concerning the presence of opsonins in immune serum. Later they introduced to medical practice the view that the autogenous vaccine, carefully administered with frequent tests for opsonin control, would be the solution to all problems of disease or disability arising from acute, subacute, or chronic bacterial infections. This phase of bacteriological work may be seen in perspective as the beginning of a period when the pathologist was required to give personal attendance to the patient in order to study his general condition as well as the properties of his body fluids. This period, which may be called the "vaccine era," had an innings of about a quarter of a century, until accumulated experience had shown that such therapy had not the value in everyday medicine which its originators, with all honesty of mind, had anticipated.

In 1908 Bela Schick introduced the dermal test for susceptibility to diphtheria. Then there were the various tuberculin sensitivity tests of von Pirquet (1907) and Mantoux (1910). In 1924 the Dicks announced their test for determining individual susceptibility to scarlet fever. The carrying out of these tests was originally the function of a clinical pathologist, but wide application and constant practice have now made such tests an everyday procedure which can be performed by any doctor who acquires the small amount of skill necessary to make a neat intradermal injection. The natural corollary of these tests for susceptibility was the development of measures for the control of epidemic and infectious diseases, including

the devising of methods for immunization as well as for dealing with the problem of "carriers" and the control of epidemics. Advances in this field have had the effect of returning much of the bacteriological work of the clinical pathologist from the patient—a position demanded by the vaccine era—to a fully equipped laboratory where the exact and intricate procedures associated with epidemiological problems can be impersonally performed.

Thus the work of Rebecca Lancefield (1933) in differentiating haemolytic streptococci by serological methods, the publications of Felix and Pitt (1934) on the antigens of *Bact. typhosum*, the development of phage-typing, the devising of selective culture media, and other purely laboratory devices have meant that the work can be efficiently and economically performed only in centralized laboratories which hold stocks of the multiple and sometimes rare sera, and all the other necessary paraphernalia. The stimulus for the creation of central laboratories was given by the 1939-45 war, and the organization then set up has been incorporated into the National Health Service as the Public Health Laboratory service, which is equipped to deal with all bacteriological and epidemiological problems, as well as the serology of infectious diseases.

Chemical Pathology

With chemical pathology the story has been different. This branch of clinical pathology has at the present time come to form a very large part of the specialists' work. At the turn of the century the subject had reached the side-room stage, mainly with qualitative tests for urinary abnormalities, whilst Ewald, Boas, and Einhorn, in the last decade of the nineteenth century, had devised crude methods for investigating gastric function. These, however, were not generally practised until Rehfuess in 1914 advocated the fractional test-meal, the potentialities of which were exploited by the Guy's school in the years after the 1914-18 war, by Hurst, Ryle, Izod Bennett, Baird, and others, who perfected the technique of gastric analysis, indicated the scope as well as the limitations of the test, and introduced the important practice of histamine administration.

In contrast, the correlation of blood chemistry with excretory chemistry had almost no foundations in the nineteenth century. To Abderhalden, van Slyke, Folin, Wu, Stanley Benedict, and others we owe the development of blood chemistry, after the practice of venepuncture had come to be regarded as commonplace and following upon the perfection of colorimetric methods of estimation. Carbohydrate metabolism has always lent itself to chemical methods of investigation. Hugh MacLean's micro-methods for blood analysis and his technique for sugar tolerance, published in 1921 in collaboration with de Wesselow, can be regarded as landmarks—likewise van Slyke's methods for detecting acidosis, published from 1917 to 1919, as well as his methods for investigating renal function such as the urea-clearance test. General metabolic investigations had begun in the 'nineties with the work of Atwater, with whom Francis Benedict worked, so that the latter came to publish the first practical method for estimating basal metabolism in 1918.

But the event which inevitably brought the chemical pathologist to the bedside was the discovery of insulin by Banting, Best, and J. J. R. Macleod in 1922. The more complete understanding of carbohydrate metabolism and the significance of glycosuria which previous work established had to be fully exploited in order to be sure of an accurate diagnosis before using a specific remedy which could be as lethal in wrong dosage or when wrongly applied

as it could be curative when properly used. Each diabetic came therefore to need individual investigation for purposes of stabilization and control and for the ordering of the rest of his life. Under modern hospital conditions much of this control can be impersonal so far as laboratory examinations are concerned, but in the smaller districts such work has generally come into the hands of the local clinical pathologist—likewise with the investigation of cerebrospinal fluid, renal function, liver function, gastric function, fat metabolism and balance, basal metabolism, and the various enzymatic changes that have been found to be associated with malignant or other changes in particular organs, as well as the complex problems of coagulation of the blood which involve many chemical procedures.

This subject, then, has made vast strides in the first half of the century, and, since the basis of all physiological function must be chemical change, it can be anticipated that the chemical pathologist will play a greater and greater part in the future in the diagnosis, control, and cure of somatic disease.

Morbid Histology

Morbid histology, being a branch of pathology which lends itself to academic laboratory study, had naturally developed to a considerable degree in the nineteenth century following upon improvements in the construction of the microscope, in methods for section-cutting, and in the development of differential and specific staining. During the past fifty years this aspect of pathology has come to have a more immediate application at the bedside or in the operating theatre, in that the scope of surgical intervention can be greatly influenced by the nature of a pathological process, whilst exact diagnosis often depends upon the histology of a biopsy specimen. Furthermore, there is now a clearer appreciation of the fact that specific and differential staining is entirely a function of the chemical composition of the tissue which selects the differential stain. This has opened up the subject as a means of studying the chemical physiology and pathology of the body tissues.

Much of morbid histology is concerned with the diagnosis of malignant disease, which, in the present state of knowledge, has a prognosis largely governed by surgical intervention at an early and operable stage. Hence the morbid histologist is in frequent demand for a rapid diagnosis and for general biopsy work. This, in great centres, is largely concentrated in separate departments, but in country districts the task falls to the lot of the general clinical pathologist and may occupy a great deal of his time. The work requires considerable experience, such as may be acquired only by long training in a big institution. With such training a correct opinion demands little more than a quick examination in some 90% of the work. The remaining 10%, the unknown quantity, may remain unsolved, with conflicting expert opinions, until the course of nature has revealed the true significance of the pathological changes.

Haematology

At the beginning of the century the science of haematology had begun to evolve. Methods were available for a simple and relatively accurate determination of haemoglobin (Gowers, Haldane) and for the enumeration of red cells and leucocytes, whilst Ehrlich's triacid stain (published 1877), which had first differentiated the granular cells of the blood and led to the technique of the differential

count, was coming to be replaced by the eosin-methylene-blue combinations, of which the first—Romanowsky's stain—was described in 1891, followed by the well-known Leishman stain in 1901. But in those days haematology was simple. The frankly leukaemic forms of the myelogenous and lymphocytic varieties of leukaemia could be recognized. The anaemias were regarded simply as primary or secondary, according to whether the cause (often haemorrhage) was known or not, whilst pernicious anaemia, then classed as primary, was identified by the high colour index and by the gross corpuscular abnormalities of the terminal stages which are never seen to-day.

Even in a general hospital the performance of a blood count was something of an event; it was done by a pathologist who usually had little interest in the clinical aspect and whose facts and figures served the physician to orientate the case as primary or secondary. Through the fifty years of this century there has been a vast accumulation of knowledge concerning the blood changes which may be associated with almost every disease, so that a blood count has come to be almost a routine, especially in patients in whom the diagnosis is not clear or in whom progress has to be watched. The value of a competent and complete morphological examination of the peripheral blood has been established by the work of such men as Naegeli, Schilling, and Arneth. Many events have arisen which have gone to make haematology almost a separate science, notably the multiplicity of techniques. The perfection of these has shown, for example, the significance which may be attached to a close examination of the dimensions of the red cells, the intricacies of haemoglobin metabolism, and such non-specific features as the sedimentation rate—itself often performed as a side-room examination. The development of knowledge concerning coagulation has increased the field of essential control tests in both medical and surgical disease.

The skill and constant practice required to carry out the time-consuming procedures neatly, accurately, and precisely are beyond the compass of the general physician, whilst the best interpretation of results is possible only to those who have a full knowledge of the clinical aspects of disease and who are steeped in the ever-changing literature of the subject. The haematologist must also be aware of the many extraneous conditions which may lead to minor and even major alterations in a blood picture, and most of these can be ascertained only at the bedside. Certain it is that a blood examination badly or inaccurately performed is more of a menace than a help, whilst if the result is interpreted without due care the deductions may be dangerously misleading.

As with chemical pathology, so with haematology. The outstanding therapeutic discovery by Minot and Murphy, announced in 1926, of the curative effect of liver in pernicious anaemia translated haematology from being an interesting laboratory subject to being a bedside procedure for the accurate diagnosis of pernicious anaemia and for the exercising of exact scientific control upon the effects of treatment. No physician can now be satisfied with the cure and maintenance of a case of pernicious anaemia without supporting evidence from his clinical pathologist. And this has shown that there are wheels within wheels, that though all cases of pernicious anaemia exhibit a megalocytosis, not all those which exhibit megalocytosis have pernicious anaemia. The diagnosis and treatment of such cases present intriguing and fascinating problems which only the expert clinical haematologist, in the closest association with his clinical colleague, can successfully solve. Bedside haematological control is now an

essential part of treatment involving any of the drugs known to have a toxic haemopoietic effect, whilst the constant watch which has to be kept on all who are exposed to irradiation hazards has, in these days of atomic energy, led to an enormous demand for skilled clinical haematologists.

One more stone, albeit an important one, in this edifice of co-operative clinico-pathological work was added when Arinkin in 1929 outlined the possibilities associated with an examination of the marrow from samples obtained by the simple operation of sternal puncture. Before that time the study of blood disorders had been confined almost entirely to samples of the peripheral blood supplemented sometimes by an examination of the marrow at necropsy, by which time degenerative autolytic changes have occurred which obscured the essential features required for fine structural differentiation. It has been said that in earlier days the great haematologist Wilhelm Türk (1871-1916), when asked to comment upon bone-marrow findings as compared with the results obtained from a blood examination, observed, "Sir, I am a peripheral haematologist." Now, in 1950, a marrow examination is regarded as a commonplace, whilst an expert opinion upon the cytology and architecture of the marrow is an essential procedure in many anaemias, as well as in obscure bony lesions. The analysis of the cytology of such samples calls for expert opinion, which in turn must be closely correlated with both the peripheral blood and the clinical findings in all cases when the result is not diagnostic.

In 1900 Landsteiner divided human blood into three groups according to the iso-agglutinin content, whilst his pupils, Decastello and Sturli, added the fourth group in 1902. It was not, however, until 1910, when Moss's paper gave wider publicity to this important matter, that blood transfusion began to be practised, making its real entry into everyday medicine as the result of experience in the 1914-18 war. Faith in this simple Landsteiner classification endured for almost thirty years, but was rudely shattered by the implications arising from the discovery and investigation of the Rhesus factors by Wiener, Peters, Landsteiner, Levine, Taylor, Race, Fisher, and others from 1940 onwards. In the past decade the development of what is now known as immunohaematology, in itself almost a subdivision of the main subject, has made the art of blood transfusion so complicated a procedure and has imposed so many scientific controls and investigations in pregnancy, in haemolytic anaemias, diseases of newborn infants, and in cases of multiple transfusion that only a handful of experts aided by geneticists can understand all the ramifications. The everyday control of such matters and the essentially practical aspects are the functions of the clinical pathologist in close association with the National Transfusion Service, which has a centre in every Region.

The Clinical Pathologist

An interesting aspect of clinical pathology, among all this welter of scientific advance, has been the evolution of the clinical pathologist himself, especially his eventual establishment within the practising profession as an essential figure in consultant and specialist work. The development of status has been different according to whether the clinical pathologist has been attached to a large teaching hospital or has been a member of the staff of one of the many non-teaching hospitals which serve such large sections of the population throughout the country.

At the beginning of the century and for upwards of twenty years the pathological department of even a teach-

ing hospital was on the whole poorly equipped, whilst the posts were usually ill paid; much of the revenue had to be derived from the rewards for hack work which the department performed. The clinico-pathological section formed but a small part of the main department, which itself was largely concerned with academic work, teaching, post-mortem examinations, and morbid histology. The routine bacteriology, haematology, and biochemistry from 1900 to 1910 at first required a staff of no more than one or two, assisted by a technician. Such men rarely penetrated to the wards, save for the collection of a specimen. Their work was mainly bacteriological owing to the rapid advances that had been made in this subject during the eighteenth century; their status was low even in their own department. Even as late as 1920, with all the extension of clinical pathology that had arisen from the experience of the 1914-18 war, it was not uncommon for most of the work to be concerned with samples of excreta brought to the laboratory, sometimes through a hatch, by the clerks and dressers of the clinical firms. From 1918 onwards the importance of clinical pathology grew apace with the expansion of haematology and biochemistry and with the necessity for scientific control, which has constantly to be exercised over bedside problems. Bacteriological work, which in the first half of the century had found such a prominent place, began to return to the laboratory itself and eventually to become centralized in fully equipped Regional centres.

It was at this phase, in the 1920's, that it came to be recognized that the personality of the pathologist, as well as his skill, was necessary at the bedside for the proper solution of diagnostic and therapeutic difficulties. This attitude has ripened through the past twenty years in parallel with the increase in size of clinico-pathological departments, most of which are nowadays themselves subdivided. The biochemist, the haematologist, and the histologist are now always welcome in ward or theatre. The men who in this century have come to practise these arts have the mentality which delights in the precision and accuracy of a laboratory procedure and at the same time gets inspiration and benefit from the human and clinical aspects of a case; the discipline of the laboratory has been found to be a fine training for interpreting the significance of findings, whether these be laboratory or clinical. By the constant performance of tests their limitations and their snags come to be appreciated together with all the features which may invalidate a result, including some which can be observed only by personal attendance upon the patient. This is the unanswerable argument to those who think that clinical pathology demands no more than the submission of a specimen, perhaps through the post, and an impersonal examination by a competent technician.

In all large hospitals the various divisions of clinical pathology have now become separated into specialties, in the same way as clinical work. Just as there are cardiologists, gastro-enterologists, and endocrinologists, so there are biochemists, haematologists, bacteriologists, and others, each pursuing a branch of what at one time was one subject. But not so in the smaller centres, where the clinical pathologist still combines all branches of the art just as his clinical colleague still practises as a general physician. The evolution of clinical pathology in these small centres has been almost an epic. Beginning in some small room, generally in the basement or an outhouse or a hut, or any unwanted premises, and often initiated by some keen and far-sighted general practitioner, the clinico-pathological service of these small hospitals and districts has been created despite financial stringency and often lack of

encouragement, and has become in many instances the central focus of the district. The clinical pathologist has often become the key consultant of the community to general practitioner and consultant alike; an artist with the needle (and what a mess a clumsy venepuncture or lumbar puncture can be); knowledgeable about modern advances and with a laboratory which, like its larger counterpart in teaching hospitals, is usually a meeting-place for intellectual medical discussion. Here, over the inevitable cup of tea, the medical men of the district come to discuss their problems, to seek advice, and to keep themselves up to date.

A landmark in the evolution of clinical pathology in this country was the foundation of the Association of Clinical Pathologists in 1927. There are similar organizations in the United States and in other countries, whilst the formation of a European Association was completed in 1947. In England, the association was started by a group of men drawn largely from the non-teaching hospitals of the Provinces, who desired to have a society where there was emphasis on the practical aspects of pathology as applied to the bedside. The association is now one of the most flourishing in the country and publishes—in co-operation with the British Medical Association—its own journal.

The further development of the fascinating subject of clinical pathology will be an important aspect of the National Health Service. Though some of this work, especially bacteriology and histology, can be done in Regional laboratories in an impersonal manner, there will always be a far larger amount which necessitates the bringing of the patient to the pathologist or the pathologist to the patient. This, in places where distances are large and the population scattered, presents many problems. In this country, happily, the evolution of clinical pathology has not led to an attitude of mind where the patient becomes a mere number attached to a wad of routine laboratory reports among which, with a fine disregard for economic factors and intelligent selection, one result may occasionally be found which supplies a diagnostic finding. Fortunately, those who have practised the subject have been at pains to see that the personal side has prevailed, so that a clinical examination has orientated the laboratory work and the patient has remained a human problem. It is to be hoped that nationalization will not alter this typically British tradition, but there is inevitably a danger that bureaucracy may insidiously submerge humanitarianism and come to regard all clinico-pathological problems in terms of the appropriate Government form. Should this come to pass, then the fine traditions of the past half-century will disappear for ever.

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Speech as a Septic Influence.—"Professor Flüge . . . might quote the same text in support of the doctrine which he preaches that speech is a means of distributing disease germs. He has shown that from the mouth of a person who is speaking come bacteria contained in little bubbles of saliva, which after remaining suspended some time in the air are scattered through the surrounding atmosphere. . . . One may conjure up a prophetic vision of the twentieth-century surgeon with antiseptic mask, beard-bag, gloves, and sterilized robe, operating within a glass sanctuary into which no one is admitted except after the fullest disinfectant lustration." From an annotation in the *British Medical Journal* of February 17, 1900 (p. 401).

PREVENTION AND CONTROL OF INFECTION

BY

ROBERT CRUICKSHANK, M.D., F.R.C.P., D.P.H.

Professor of Bacteriology, St. Mary's Hospital Medical School

A few years ago C.-E. A. Winslow, the doyen of preventive medicine in America, wrote a book called *The Conquest of Epidemic Disease*. Although the title sounded rather pretentious and euphemistic, Winslow's object was to trace the development of epidemiological concepts about the causation of epidemic disease from the time of the biblical belief in visitations from heaven or hell, through the theories on spontaneous generation and miasms, to the present-day proof of the transmissible germ; to show, in fact, that, since the aetiology and modes of spread of most epidemic diseases were now known, the means for their control should be available.

Beginning with the acute observations of Hippocrates in his *Airs, Waters, and Places* on the epidemiology of such conditions as the ague, dysentery, and chest infections, the road to knowledge of the causation of infectious diseases has been slow and tortuous, and was blocked for a thousand years during the "Dark Ages." The pandemic of plague in the fourteenth century, which was so obviously contagious, was followed by a pandemic of syphilis about A.D. 1500 which allowed Fracastorius to elaborate his clear and convincing principles on the spread of disease by contagion, although he conceived the transmissible agent as being gaseous rather than living particulate matter. In spite of Kircher's scientific arguments in favour of the "contagium animatum" and Leeuwenhoek's microscopical demonstration of the little animalcules in the seventeenth century, the germ theory was again stayed during the eighteenth century, largely by Sydenham's advocacy of the "Epidemic Constitution," and it was not until the latter half of the nineteenth century that the genius of Pasteur and the painstaking researches of Koch firmly established the microbial aetiology of infection. By 1900 the heyday of bacteriological discovery had passed, for the causal organisms of most major pestilences—typhoid, dysentery, cholera and plague, tuberculosis, pneumonia and diphtheria, meningitis, and gonorrhoea—had been identified.

But there still remained many puzzles. The aetiological agents of typhus, syphilis, yellow fever, scarlet fever, and whooping-cough were still undetermined, while the occurrence of infection among those who had no obvious contact with the sick, and, *per contra*, the failure of others to develop infection in spite of such close contact, were still unexplained phenomena. The importance of the carrier in the spread of infection, the principles of immunology, and the factors determining the virulence of an organism are developments of the past half-century. At the beginning of the twentieth century there was still a great deal of spade-work to be done in the methods of isolation and identification of specific pathogens, so that opportunities for devising new microbiological techniques abounded. The typhoid bacillus was separated from the colon bacillus by fermentation reactions, the bovine type of tubercle bacillus was differentiated from the human type, and the botanical classification of bacteria as agents of infection became an absorbing study for the rank and file of the new race of bacteriologists who were still closely attached and subservient to the morbid anatomists. However, men of ideas like Ehrlich, Bordet, Almroth Wright, and Theobald