Potentials in Pathology

An Inaugural Lecture

GIVEN IN THE UNIVERSITY COLLEGE OF RHODESIA AND NYASALAND

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POTENTIALS IN PATHOLOGY

THE definition of pathology which is given in most textbooks of the subject, in most dictionaries, and in the *Encyclopaedia Britannica* is 'the science of disease'. This may be accurate but it gives little idea of the scope of the subject and the observant student will soon notice that he is being shown patterns of disease in the wards and clinics as well as in the Pathology Department. Why, then, should the term pathology be used for one particular course in the medical curriculum? The *Oxford English Dictionary* gives no less than four meanings for the word, the first of which is more helpful than our original definition. Pathology is 'that department of medical science, or of physiology, which treats of the causes and nature of diseases, or abnormal bodily affections or conditions'. This can be expanded to state that the scope of the subject is the study of the structural changes found in the organs of diseased persons before and after death, of the functional disorders associated with these changes, of the adaptations made by the diseased and other organs to compensate for the damage, and of the causes of these changes and disorders. You will have noted that the expanded definition refers not only to diseases but also to 'abnormal bodily affections or conditions'. Disease, in the conventional sense, is only a province, albeit a major one, of the pathologist's field, for he is also interested in congenital deformities, mechanical injuries, chemical intoxications, and those innate or acquired susceptibilities which affect resistance to other agents of disease.

It is the object of this lecture to discuss the role of an academic department of pathology in Central Africa, as

seen through the eyes of a recent arrival in this country. Like all other academic departments this one has two functions, to teach and to pursue original research; and in common with other clinical departments it will also have responsibilities towards patients, in this instance, of a diagnostic rather than a therapeutic nature. My principal concern is with the contributions which the department might make towards the acquisition of new knowledge. In order to be able to discuss the possible fields of investigation it is necessary to spend some time outlining the different approaches which can be made. This can be achieved by looking at the evolution of the subject.

Historically the first way in which disease was studied was by the dissection of corpses after death. This was a natural development in the attempt to ascertain what was wrong with the patient, what had killed him, and if the diagnosis which had been made during life was correct. Early publications on morbid anatomy, which is the morphological study of disease processes in the gross as seen at post-mortem, or in the diseased tissues and organs removed from the living body by a surgeon, were published in the sixteenth and seventeenth centuries but were not of a systematic nature. Nevertheless, Bonet (1620–89) in 1679 published his *Sepulchretum* which contained descriptions of about 3,000 post-mortems drawn either from the writings of earlier physicians or from personal observations. However, at this time there was no serious attempt to correlate the patient's symptoms during life with the post-mortem appearances. This did not occur for nearly another 100 years when Morgagni (1682–1771) published his *De sedibus et causis morborum* in 1760. In this work Morgagni recorded the life history of his patients, the history of their diseases, the events in the final illness and in death, the autopsy

findings and, furthermore, attempted to correlate the symptoms during life with the pathological findings after death. He made a number of first observations which are of importance, including those of tuberculosis of the kidney, of pneumonia, and of hemiplegia. The first systematic textbook dealing exclusively with morbid anatomy was published in 1793 by a Scot, Matthew Baillie (1761–1823), who was a nephew, pupil, and heir of the famous William Hunter. One of the important points about Baillie's work, *The Morbid Anatomy of Some Important Parts of the Human Body*, is that this was the first occasion upon which an author worked from the organs and the changes therein towards the patient's symptoms rather than the other way about. Baillie also published an Atlas illustrating the changes which he had found. During the early part of the nineteenth century morbid anatomy flourished successively in France, England, Ireland and thereafter, for a period, in Vienna. The first chair in the subject was established in Strasbourg in 1819 and its first occupant, Lobstein, was the first person to use the term 'pathogenesis', that is the manner of development of a disease; furthermore, he was particularly interested in functional pathology rather than in the static appearances of the organs and tissues at the time of the patient's death.

Further developments of the morphological science of the study of the tissues and of the correlation of pathological lesions with disturbance of function had to await the development of the cell theory and the technical development of the microscope. The cell theory was advanced in the middle of the nineteenth century particularly by Schwann (1810–82), a noted German anatomist, who published his major work in 1839. A compound microscope had been invented by Galileo in 1609 as a by-product of his

invention of the telescope but it was not effective and for many years simple lenses of high magnification were used. It is interesting to note that with this apparatus Malpighi (1628–94) was able to describe the microscopic appearances of the skin, the spleen, and the liver as well as the development of the heart and the nervous system. But it was some time even after the introduction of the cell theory before many pathologists applied even the simple microscope or the high-power lens to the study of diseased tissues. Thus Rokitansky (1804–78), one of the great pathologists of the last century, whose handbook of pathological anatomy was based on 30,000 personal post-mortems and something over twice that number of records from the Allgemeines Krankenhaus at Vienna, made very little use of the microscope and in fact attempted to resuscitate the classical humoral theory of disease.

It was Rudolph Virchow (1821–1902), the greatest of all pathologists and the first professor of pathology in Germany—at the University of Würzburg and later for many years at Berlin—who first seriously applied the microscope to disease processes. In 1858 he published his famous book *Die Cellularpathologie*, which made possible the successful foundation of a systematic rational science based on both naked eye and microscopic observations. In this work Virchow accepted the cell as the unit of the body in health and disease, considered that disease of an organ was, in reality, disease of its individual cells and regarded pathological changes as being merely abnormal manifestations of otherwise normal processes. In his long life Virchow studied numerous pathological processes, established an outstanding school of pathology and founded, in 1847, the journal which still bears his name—*Virchow's Archiv für pathologische Anatomie und Physiologie und für Klinische*

Medizin. The title of this journal indicates the breadth of Virchow's approach to his subject: this is underlined by the statement made early in his career that 'pathological physiology is the main fortress of medicine, while pathological anatomy and the clinics are outlying bastions' (Boyd, 1963). Although he had no microtome, no stains for the earlier part of his life, no formalin fixation until 1893, and no embedding media until late in his work, he stated, towards the end of his life 'we must endeavour to dissect the cell, to take it apart and find out what each portion contributes to cellular function and how these parts go wrong in disease' (Boyd, 1963).

Thus morbid anatomy became inseparably linked with morbid histology, that is the morphological study of disease processes by microscopy. Morbid histology or histopathology, is now the stand-by of the diagnostic pathologist and is the method which is used invariably in the examination of tissue specimens resected by surgeons and of similar material obtained from a post-mortem. With the increasing complexity of the medical course there has been a regrettable tendency for morbid histology to be divorced completely from normal histology, that is the microscopic study of normal tissue. It is our intention in this medical school to stop this bad habit. Our students in their class in normal histology are being taught in part by pathologists and are being shown selected sections of pathological processes at the same time as they are studying normal tissue. In this we are following the precedent set by Hughes Bennett (1812–75) who was one of the early lecturers on normal histology at the medical school in Edinburgh and in whose course there were microscopical demonstrations of morbid histology. The value of this multidisciplined approach to medicine is illustrated by the fact that

Hughes Bennett described the first recognized case of leukaemia.

During the past few decades there have been enormous technical advances in the histological sciences. Whereas previously tissue components were recognized empirically by their ability to react with vegetable dyes, the application of accurate chemical, immunological, and physical techniques under vastly improved conditions of fixation has made it possible to identify with certainty many proteins, carbohydrates, and lipids at tissue and cellular levels. Certain substances can now be estimated quantitatively at the μg and even mμg level. Subtle variations of these techniques are even making possible the accurate identification of substances seen at the enormous magnifications of the electron microscope. Thus, the tissue section, when ready for examination in a research project, frequently represents the interplay of three or four physical and biological sciences.

Let us turn now from the description of pathological changes in the tissues to some of the agents which cause these changes, in other words to bacteria and related micro-organisms. It is clear that the description and recognition of micro-organisms had to await the perfection of some form of magnifying apparatus sufficiently powerful to enable them to be visualized. It is therefore quite surprising to recall that the first bacteria were described as long ago as 1683 by van Leeuwenhoek (1632–1723), who was one of the first to produce a simple microscope; this was a high-power magnifying lens rather than the compound microscope with which we are familiar today and which was not introduced until about 1830. van Leeuwenhoek described and illustrated six species of micro-organism from the human mouth of which five are recognizable as species

which are known today. Just how outstanding was his ability and industry can be understood when I remind you that during the next 150 years only occasional descriptions of micro-organisms were made; nevertheless by the mid-nineteenth century the existence of bacteria was widely accepted.

The next step was proof that some microbes cause disease and the first advance of this nature was made in 1835 by Bassi (1773–1856), a lawyer who became interested in biological phenomena and who recognized that the disease muscardine of silkworms was due to a fungus. At this time it was still widely held that many infectious diseases were due to a miasma, one of the 'subtle exhalations from the bowels of the earth or arising from the air' (Singer and Underwood, 1962). At about this time Henle (1809–85) published a fascinating essay entitled *Von den Miasmen und Kontagien*, in which he divided infectious diseases into three groups. The first he believed to be due to a miasma alone; in this group he included malaria. The second group he believed to originate from a miasma but thereafter a living parasite developed in the body, multiplied there and was responsible for the spread of the disease by infection; this group included most of the common infectious diseases. In the third group were a few diseases, including syphilis and scabies, which were believed to be due to contagion alone. This far-seeing work laid down the principles of the specific origin of infectious diseases but it was another nine years before any bacterium responsible for a human disease was described and the great majority were not discovered until much later in the century. Indeed, you will find smallpox listed as a miasmatic disease in the Public Health Report of Southern Rhodesia for 1902–3. Progress was to a large extent hampered by unsuccessful attempts to

disprove the theory of spontaneous regeneration; even up to 1860 this theory still had many supporters. Furthermore, despite clear descriptions of the yeast cell by Schwann in 1837 and by others, it was still generally believed that fermentation, although known to have much in common with infection, was a purely chemical process.

It fell to Pasteur (1822–95) to clear up much of this confusion. After studying the fermentation process in detail and showing quite clearly that this was due to organisms carried in the air and not to a purely chemical process, Pasteur went on to show, in a conclusive series of experiments, that the air contained micro-organisms, that these organisms were alive and could cause putrefaction, that access of air but not of organisms to a putrescible infusion caused no putrefaction, and finally that micro-organisms were not uniformly disseminated in the air. The major diseases with which Pasteur's later work was concerned were anthrax and rabies so that he was not only a bacteriologist but also one of the earliest virologists. He established the principle that attenuation of the virulence of both the anthrax bacillus and the rabies virus was possible and that these attenuated organisms could protect animals and man against subsequent inoculation of virulent material. These observations, along with those of Jenner on vaccination against smallpox and of Kitasato on antitoxins, led to the development of prophylactic immunization from which was to develop, many years later, the comparatively new science of immunology, the techniques of which are used extensively by experimental pathologists today.

Contemporary with Pasteur was Koch (1843–1910), whose studies laid the basis of the techniques by which microbial diseases are now studied and established bacteriology as a science. In addition to discovering the bacillus

which is the cause of tuberculosis he identified the cholera bacillus and that terror of modern hospitals, the staphylococcus, which causes serious wound infections and can be resistant to most of the modern antibiotics. Koch's name is also associated with the famous postulates which are still the tests by which the pathogenicity of an organism is established. To prove that a micro-organism is the undoubted cause of a disease it must be demonstrated, first, that the organism is constantly present in every case of the disease; secondly, that a pure culture of the organism can be prepared from a patient with the disease and that this culture can be maintained for repeated generations; and, thirdly, that the disease can be reproduced by means of a pure culture removed by several generations from the organism first isolated from the patient. Virchow made the penetrating comment on these postulates that the discovery of the cause of a disease does not resolve the problem of what that disease really is. He was of the opinion that the pathogenesis of an infectious disease would be fully understood only when bacteriological discovery was related to cellular and organismal interaction. Nevertheless, Koch's postulates have been fulfilled for many diseases, though it must be clear that the third test can be applied only to those conditions to which animals other than man are also susceptible. This is not possible for all micro-organisms, for there are animals which are not susceptible to bacteria which infect man. However, there exist organisms closely similar to those causing human diseases which are pathogenic for animals so that, by studying the life history of these organisms and their effects in animals, valuable sidelights can be thrown on allied diseases in man. Furthermore, not all men are subject to all human infectious diseases; this is due to a state of immunity, to which I shall refer in more detail

later. First, however, it should be noted that the subsequent development of the science of bacteriology has led to the discovery of specific organisms for the great majority of human infectious diseases, to studies on the differentiation of closely related micro-organisms and to the recognition that micro-organisms can mutate under a variety of circumstances such as the administration of bactericidal and bacteriostatic drugs to give rise to resistant strains. This in turn has led to a major subdivision of the science, namely microbial genetics. It is now also true that the study of viruses is a sufficiently complex process, requiring special knowledge and techniques, that virology itself is now another separate division of pathology. Indeed, both bacteriology and virology are sufficiently broad in their scope that only those aspects of them which are related to medicine come within the province of human pathology.

I have discussed the evolution of the morphological aspects of pathology and of microbiology at some length in order to indicate the complexity of the science of pathology. But this is not all. In studying abnormal states it is frequently necessary to use the techniques of the biochemist. This has led to the development of chemical pathology, sometimes called clinical chemistry and often erroneously included in the overall term biochemistry, as a division of pathology of equal status with those which have been described. The study of the chemistry of the blood is included in chemical pathology, but the morphological study of the cells of the blood and of the development of these cells, of the complicated process of coagulation of the blood and of blood grouping and all the other manipulations involved in blood transfusion represents yet another branch of pathology, namely haematology. Furthermore, in a country where parasitic infections are common,

the expert opinion of a parasitologist is indispensable in any department of pathology. Lest I be accused of empire-building let me assure you that all of these divisions of pathology are to be found in every medical school in the tropics and that the decision to have them all in a single department was not mine. You will now appreciate, however, that this department must be bigger than most others in the Medical School or, for that matter, in the rest of the College. The teaching and diagnostic load which the Department must undertake will be possible only if all the major branches of the science are represented by at least one member of the academic staff.

Let us consider now some of the research problems which might be studied in the Pathology Department of the College. In doing so there is a general point which I should like to make before discussing any of the problems in detail. The Nuffield Report upon which so much of our thinking and planning has been based states (Second Report of the Medical School Planning Committee, 1959) that 'the direction of medical research should be determined by the conditions of the country' and that 'projects should be chosen which exploit local resources and which are complementary to, rather than duplications or direct extensions of work being done in the United Kingdom or the United States. Those requiring very elaborate and expensive apparatus and highly trained technical staff for its use and maintenance, should, on the whole, be avoided.' These are statements which I and my colleagues in the Faculty of Medicine fully endorse. I believe that one might go even further and state that our research should be determined not only by the conditions of the country but by those diseases which are found in the majority of the population of the country. Thus I believe that those of us whose

previous interests were diseases which are not important or common in this country should turn from those subjects to apply the knowledge and expertise which we may have acquired to problems which do exist in this country. There are many investigators working in countries such as Britain and the United States in large, expensively equipped and well-staffed laboratories on diseases such as cancer of the lung, coronary thrombosis, and many of the other diseases which are common in Europe and America. I believe that it would be morally wrong for those of us who have accepted appointments in this country to continue research in fields such as these. There are all too few research workers who are studying the major disease problems of this and other countries in Central Africa and fewer still who work in these countries. I believe that I speak not only for myself but also for my colleagues when I say that our hope is that any research which we may do during our stay here will be of benefit to the population of this country as a whole. As I see it then, the major problems in which the Pathology Department is likely to be interested in the next few years include bilharziasis, other helminthic diseases, nutritional diseases, tuberculosis, virology, and what is nowadays called geographical pathology. I propose to say something about each of these to indicate the lines along which I believe that useful research could and should be pursued; in doing so it is only fitting that I should mention the contributions which may have been made already by workers in this country.

There is no need to tell a Rhodesian audience that bilharziasis is common but there are many aspects of the disease that are still little understood or require clarification. Gelfand, in his book *Livingstone the Doctor* (1957), credits Livingstone with the first description of the disease in

Central Africa and also mentions a report by Patton that the disease was common in Gwelo in 1898. This is supported by other statements in the early Public Health Reports of the country. Thus the Salisbury District Surgeon is quoted in the Report for 1915 as stating that 30 per cent of all Africans in the jail were affected (Fleming, 1916). Since that time there have been a number of studies of the prevalence of the disease in different parts of the country and it is now clear that this statement was an underestimate. Thus, recent surveys of several African communities carried out by the Bilharzial Research Laboratory in Salisbury have shown that, at the ages of maximum prevalence, the incidence of infection with *Schistosoma haematobium* varies from 39 per cent in regions supplied by piped water to 98 per cent in regions under irrigation; in the same regions the incidence of infection with *S. mansoni* was 6 per cent to 9 per cent (Clarke, 1965).

There have also been conflicting statements about the importance of the disease and the likelihood that it could be brought under control. Thus Fleming (1922) stated in the Public Health Report for 1921: 'the protracted history of this disease and its after effects have in the past rendered it one of the most serious of the helminthic infections, but the discovery by Leiper of the intermediate host in certain varieties of fresh water snails and the results obtained by Archibald in Egypt and by others in the treatment by intravenous injections of tartrate of antimony have robbed it of much of its danger'. Statements such as this have followed many of the new discoveries in relation to the disease and can be found in subsequent Public Health Reports. Thus Martin stated in great optimism (1946) 'the antigen skin test and the syringe treatment of the disease have undoubtedly solved something more than half of our

bilharzia problem. As a result of the application of these new methods in rapid diagnosis and speedy and effective treatment, the incidence of the disease is already showing considerable diminution; there does not appear to be any reason why within the next few years this particularly disabling disease should not be entirely eliminated'; but by 1957 Morris was writing, 'in Southern Rhodesia the situation is rather static and little progress has been made using the weapons at present available to control the molluscan intermediate host'. Optimism was again shown in 1959 when Blair wrote: 'after years of frustration and disappointment at long last methods and materials have evolved that hold out promise that this disease can be practically and economically controlled'. But a more realistic view was expressed by Alves (1957) who wrote: 'when the picture over the years in Southern Rhodesia is studied, it is clear that, far from progress in the control of bilharziasis being achieved, the situation has steadily worsened. The disease claims many new sufferers every year in the African population in spite of the greater attention that is being paid to it'. This is still the situation. In the same article Alves made a plea for more co-operation between all those concerned in the possible spread of the disease such as irrigation and construction engineers, agriculturists, and public-health workers as well as medical men. The Departments of Medicine, Sociology, and Zoology in the College have already collaborated and are continuing to collaborate with the Government's Bilharzia Research Laboratory in several projects. There is every indication that similar collaboration will develop on projects under consideration in the Department of Pathology.

The first extensive piece of work on the disease in this country resulted in the publication by Blackie in 1932 of

A Helminthological Survey of Southern Rhodesia. Blackie's work involved not only the examination of human patients to determine the prevalence of the disease but also of the intermediate hosts and their ecology. This was the first of many surveys of the incidence of the disease in different districts of the country. Blackie also demonstrated the presence of the sheep organism *S. mattheei* in human beings. A few years later Alves and Blair (1949) found the incidence of the disease to be 36 per cent in European boys and 10 per cent in girls in the Umvuma–Enkeldoorn area. The establishment of a Bilharzia Research Laboratory was interrupted by the war; nevertheless, during that time, Mozely undertook a detailed study of the ecology and bionomics of snails and published his monograph *The Control of Bilharzia in Southern Rhodesia.* In 1951 this Research Laboratory was recognized by the World Health Organization as the snail reference laboratory for Southern and Eastern Africa and since that time there has been pursued in it an intensive and systematic study of malacology.

Much work has been published by Gelfand and Alves and their colleagues on the distribution of ova in various parts of the body (Gelfand, 1949; Gelfand and Ross, 1953*a*, 1953*b*; Alves, Woods, and Gelfand, 1955; Alves, 1958). These studies have shown that ova may be discovered in very many tissues and have indicated, also, the relative frequency with which ova of the various species of schistosome can be detected in the different tissues. Much of the work has been based on the detection of the eggs of *S. haematobium* and *S. mansoni*, but Alves published a particularly valuable paper in 1958 in which the distribution of *S. mattheei* was also included. All of this work has been of a qualitative nature and there does not seem to have been, here or elsewhere, a quantitative study of infection by the

various species of worm. There have been several suggestions over the years (Blair, 1956; Elsdon-Dew, 1962) that there is an urgent need for studies in which an attempt is made to assess the relationship between the worm load and the severity of the tissue damage. One way in which this information could be obtained would be by a quantitative assessment of the distribution of ova in different tissues of the body, particularly if this is correlated with the actual lesions which have occurred. This sort of investigation is likely to be time consuming but should be well within the capabilities of the Department. Studies of this kind are, of course, conducted on material obtained at post-mortem and thus may not give an accurate indication of conditions obtaining during life. It is hoped to pursue, also, the development of accurate methods of assessing the worm load in the living patient; enzymological and immunological techniques seem promising in this field.

One of the most controversial aspects of the disease is the relationship between infection and lesions in the liver. There is no question that ova, particularly those of *S. mansoni* and of *S. japonicum*, can be found in the liver and that histological examination indicates that these are frequently associated with a chronic inflammatory reaction. What is in question is the relationship between the bilharzial infection and cirrhosis of the liver. This controversy dates from the beginning of this century when Symmers (1904) published his short but classical paper on liver disease in Egypt, in which he stated, 'the cut surface of the liver looks as if a number of white clay-pipe stems had been thrust at various angles through the organ', and suggested that this particular type of cirrhosis was due to bilharziasis. For the next fifteen years there was much argument, during which it was suggested that either malaria or kala-azar, rather than

bilharziasis, might be the cause of the enlargement of the liver which is so common not only in Egypt, but elsewhere in Africa. These views were supported by the work of Fairley (1919–20) who found that the experimental infection of monkeys with *S. haematobium* or *S. mansoni* resulted in focal lesions of the liver but no change which could be regarded as the counterpart of the cirrhosis found in man. On the other hand, Fischer (1919) had found a frequent association between human infection with *S. japonicum* and cirrhosis. Thereafter many writers supported the bilharzial aetiology of cirrhosis though there were differing views as to whether the liver lesions were the result of the deposition of ova or of the diffusion of toxins from ova or from adult worms. The suggestion that toxins might be responsible arose from the observation that lesions frequently occurred in the absence of ova.

An important study was included by Gelfand in his monograph (1950) entitled *Schistosomiasis in South Central Africa*. He found that the incidence of cirrhosis of the liver in post-mortem material was no higher in Salisbury than it was in similar studies published from Kampala and Johannesburg, two places where bilharziasis is not endemic. Lesions of bilharziasis or ova could be detected histologically in twenty-three out of forty-one livers in which cirrhosis due to any cause was present. But when material from the livers of patients infected with bilharziasis was examined, one out of two such livers contained ova whatever the particular pathological lesions present. This last is a particularly important point which had not been emphasized, by previous workers. Gelfand also found that infection of the liver with ova of *S. haematobium* was more than twice as common as infection with ova of *S. mansoni*; this was a somewhat unexpected finding, for it had always

been accepted previously that the organism most likely to affect the liver was the predominantly intestinal parasite *S. mansoni*. Gelfand concluded that bilharziasis was not the only or most likely cause of cirrhosis in this country but that this condition was more likely to be due to a combination of diseases including the presence of malnutrition. In a later study of adult cases during life, Forbes and Gelfand (1962) reported that no evidence of bilharziasis was found in liver tissue from twenty-seven patients. More recently, Gelfand (1963*b*) did find bilharzial lesions in liver tissue from three out of twenty-four adults and from six out of twelve individuals in the age group 4–20. All nine of these patients had histological evidence of cirrhosis of the liver; in five of the juvenile cases the lesions were suggestive of the clay-pipe stem cirrhosis described by Symmers. Other recent workers have suggested that, although the lesions which occur so frequently in the livers of patients with bilharziasis are of a focal nature, continued heavy invasion can give rise to cirrhosis. Within the last year Cameron and his associates have made significant contributions in showing that the liver changes which occur in experimentally infected mice can be completely reversed by treatment (Cameron and Ganguly, 1964) and that the combination of bilharziasis and a protein deficient diet in rats greatly enhances the liver damage, leading to a condition not unlike cirrhosis in man (Cameron and Bhattacharyya, 1965). Further work is required to clarify the relationship between these experimental results and the picture seen in man. Thus, despite a great deal of work, the true relationship between bilharzial infection of the liver and cirrhosis of that organ has not yet been established. As in the work on the distribution of ova which has already been mentioned, there appears to have been no quantitative

study of the intensity of infection of the liver or of the types of schistosome in relation to lesions in that organ and there is clearly a need for such a study. There should be no difficulty in investigating whether those patients who have clay-pipe stem cirrhosis have larger numbers of ova within the liver than is the case in those patients who do not have cirrhosis. Recent work (Lichtenberg, 1955) has drawn attention to the frequency of lesions of blood-vessels in the liver; these require further investigation for they may play a role in the pathogenesis of the cirrhosis.

Much work has also been done in this country on the involvement of the urinary tract in the disease. This has covered such aspects as the diagnostic examination of the urine for ova (Bennie, 1949; Bennie and Blair, 1955); the use of biopsy material obtained from the bladder mucosa in the diagnosis of the disease (Gelfand and Ross, 1949), one important conclusion from which was that ova can be demonstrated in material taken from a bladder mucosa which looks quite normal on cytoscopy; the important observation by Gelfand (1950) that dilatation of the ureter is ten times as common as stricture of that structure in the disease and that hydronephrosis occurs with dilatation rather than stricture of the ureter; the possible relationship of urinary bilharziasis to the nephrotic syndrome (Gelfand, 1963*a*); a study of the relationship of chronic urinary bilharziasis to hypertension (Gelfand, 1964); and of the significance of calcification of the bladder as a diagnostic sign in the disease (Gelfand, 1950) and of the frequency of this sign in children (Gelfand, 1965). Much of the earlier work on this aspect of the disease was performed on autopsy material, but similar observations were made on living patients by Honey and Gelfand (1960). My colleagues in the Department of Medicine are anxious to pursue this

urinary aspect of the disease in greater detail than has been done previously but I believe that the Department of Pathology can also make a contribution in this field.

I refer particularly to the problem of cancer of the bladder, another subject on which there have been considerable differences of opinion over the years. The earliest paper was that of Ferguson (1911), based on a study in Egypt, in which it was claimed that bilharziasis predisposed to carcinoma of the bladder. This hypothesis was accepted and supported by many subsequent workers but Gelfand (1950) showed that the incidence of cancer of the bladder in this country was similar to that found in Johannesburg where, as indicated previously, the disease is not endemic. Furthermore, the incidence of bladder carcinoma amongst Europeans in Southern Rhodesia is roughly twice that amongst Africans, although bilharziasis is very much less common in Europeans, and the tumour is much more common in men than in women although the incidence of bilharziasis in the two sexes is roughly similar. On the other hand a recent study by Mustacchi and Shimkin (1958) in Egypt showed a significant correlation between the presence of bilharziasis and carcinoma of the bladder in males, and their results also suggest that pre-cancerous changes can be found in patients with bilharziasis. The evidence from experimental studies is also contradictory, for Fairley (1919–20) showed hyperplasia three months after infection in sooty monkeys and Edwards and McCullough (1954) claimed that a carcinoma had been produced in a baboon only twenty-six weeks after infection, whereas Shimkin, Mustacchi, Cram, and Wright (1955) were unable to obtain tumours in mice after subcutaneous injections of lyophilized ova or cercariae. The final conclusion of Mustacchi and Shimkin was that it is premature to consider whether

the relationship is directly causal or whether bilharziasis may potentiate other carcinogens.

It is relevant that Dodge (1964), working in Kampala, found a high proportion of bladder tumours in Ugandan Africans, in whom bilharziasis is infrequent but chronic urinary retention due to urethral stricture is common. He indicated that there is circumstantial evidence which suggests that the development of the tumours in the Ugandan Africans may be associated with quantitative or qualitative peculiarities in the excretion of tryptophan metabolites or with an increase in the activity of the enzyme β-glucuronidase in the bladder mucosa and that a role of chronic retention in the bladder might also be established. Similar suggestions have also been made by Egyptian workers (Mofty, 1962) who have studied the activity of β-glucuronidase in the bladder mucosa; these workers have suggested the possibility that enzymes in the bladder mucosa or in the urine may act upon conjugated substances in the urine in such a way as to release potential carcinogens. Other support for the hypothesis that bilharziasis itself is not a cause of cancer comes from the observations of Gelfand (1950) and other workers that the incidence of carcinoma of the colon and of carcinoma of the liver is not increased in patients who suffer from the disease. Here then is an aspect of this common and important disease which requires further study and which can be approached without the use of complicated apparatus or expensive techniques. This, rather than lung cancer, is the sort of project which one would like to see a cancer research fellow working on at this time in this country.

There is another major aspect of this disease which urgently needs further investigation, namely, the mechanism by which immunity develops. Many workers have

suspected that immunity to the disease develops in human beings living in an endemic area and constantly exposed to infection. This has been supported by work carried out in this country. Thus Morley-Smith and Gelfand (1960) found that the incidence of infection with *S. haematobium* decreased with age; they interpreted their observations as suggesting the acquisition of immunity in the older age groups, assuming that the exposure to infection at different ages was similar. In a much more detailed study of a number of communities, Clarke (1965) has confirmed and extended these observations. The patterns of prevalence of infection in relation to age and to intensity of infection, and differences in prevalence before and after periods of control of transmission, have established beyond doubt that man develops resistance as the result of infection. The comparison of prevalence rates determined by the examination of specimens for ova with those determined by tests for the presence of antibodies supports the concept of acquired resistance and indicates that this resistance is accompanied by evidence of immunological activity. But the precise mechanism by which resistance, or immunity, is established has yet to be determined.

Broadly speaking immunity to all infectious diseases can develop in one of two ways. You are all aware of the immunizing injections which are given in infancy and at other times of life to protect patients from specific diseases; these injections stimulate the production of antibodies which have the specific property of reacting with and neutralizing toxins produced by certain bacteria, such as the organisms of diphtheria and tetanus, or of rendering the bacterium itself more susceptible to other defence mechanisms of the body. There are other diseases, such as tuberculosis, where the development of circulating antibodies is

a purely secondary phenomenon and the immunity which develops is the result of the acquisition of certain properties by lymphocytes and other cells which are found principally in the spleen, the lymph nodes and elsewhere; this is known as cellular or cell-bound immunity.

Experimental studies have shown that mice and hamsters can acquire partial immunity to bilharziasis whereas the rhesus monkey can develop complete immunity under certain conditions. But there is as yet no evidence that a demonstrable antibody has ever been implicated in the mechanism of resistance in such experiments. Thus, the transfer of antibodies from one experimental animal to another has not prevented the second animal from infection upon exposure. It has been shown, also, that animals producing antibodies comparable in degree to those produced in infected or resistant animals are not necessarily protected against reinfection (Smithers, 1962). Furthermore, there is no evidence that those cells which are concerned with cellular immunity cross the placental barrier so transferring immunity from mother to offspring. It is, of course, difficult conclusively to demonstrate the presence of resistance in man for this can be done only by the infection of human volunteers. In a single experiment of this kind the exposure of a small group from a hyperendemic area to several hundred viable cercariae did not result in the production of ova in the stools of volunteers (Fisher, 1934). However, this result must be interpreted with caution for the species of schistosome used was one which has yet to be shown conclusively to be pathogenic to man. Similar caution must be used in accepting the conclusions drawn from two recent publications in this country. Morley-Smith and Gelfand (1958) showed that in an endemic area only two out of twenty-seven infants under the age of two had ova in urine

or stool specimens, whereas fifteen out of twenty-seven children aged 4–11 from the same area showed evidence of infection; they concluded that the apparent freedom of the infants from infection was due to the acquisition of immunity from infected mothers. In a subsequent study, Gelfand, Clarke, and Turnbull (1964) found circulating antibodies in the new-born infants of infected mothers and concluded that their results demonstrated a possible transfer of immunity. In assessing these conclusions notice should be taken not only of the remarks made above but also of the observation by Clarke (1965) that incidences of infection of 30 per cent and 89 per cent occurred in children under 4 years of age in two communities. Furthermore, the supposedly immune infants in the study of Gelfand *et al.* were not followed up to see whether they acquired infection during the relatively short period when antibodies transferred across the placenta persist in the neonate and might prevent infection if they did have a protective function.

These studies have been considered in some detail and critically in order to indicate the problems involved in assessing the mechanism of immunity in this disease. Apart from the theoretical interest of this problem there is the practical point that once the mechanism of immunity has been elicited it may be possible to undertake investigations designed to produce some form of prophylactic immunization. It is worth while recalling, therefore, that the various tests which can be used to demonstrate the presence of a circulating antibody, and which have a very practical application in the diagnosis of the disease, indicate that there are cross-reactions between the various species of schistosome and between schistosomes and other helminths. This raises the question whether preparations from

species such as *S. bovis* and *S. mattheei*, which affect cattle and are sometimes found in man (Blackie, 1932; Alves, 1949), but are thought not to produce lesions, might be used to stimulate immunity to the pathogenic species found in man.

These are just some of the aspects of bilharziasis which I hope will be studied in the Department of Pathology. There are, of course, many other aspects of this disease which will still require elucidation but in many instances these are problems for malacologists, helminthologists, biologists, or physicians rather than for pathologists. Let us now turn to some of the other problems which I believe it should be possible to study. It is in fact a pleasure to be able to tell you that some of them are already under investigation. For example, Dr. W. M. Buchanan is working on siderosis, that is the deposition of iron in the tissues, a condition which is frequently seen in Africans but is quite uncommon, if not rare, in Europeans. This condition has been studied elsewhere, particularly in South Africa, but it is clear that information is required in this country about the distribution of iron in the tissues, about the relative quantity which is distributed and about the relationship of the deposition of iron in the tissues to the concentration and mode of transport in the blood and to the iron intake of the diet. These are all problems which are currently under investigation. Mr. J. M. Goldsmid is using the research facilities of the Department in a study of hookworm disease, another common condition and one which has also attracted the interest of other workers in this country on previous occasions (Blackie, 1932). Mr. Goldsmid is particularly interested in the frequency with which different species of hookworm infect man, in the relative load which occurs and in the possibility of the development of

immunity, a subject which has not yet received the attention it merits.

Coming now to microbiology, what has the Department to offer? There are two major fields where it is hoped that work performed in the Department could be of service to the community. The first of these is tuberculosis. One has only to read through the Public Health Reports of the country to realize what a problem this has become. The position early in the century was that tuberculosis was a common disease amongst mine workers though showing no tendency to spread amongst rural members of the African population. But by 1920 pulmonary tuberculosis was responsible for one-fifth of the deaths recorded among Africans, being second only to pneumonia as the major cause of death. By 1946 pulmonary tuberculosis had become an even greater problem, with a case mortality of 25 per cent and a rapid course. The incidence continued to climb until 1959 when there were 120 cases of pulmonary tuberculosis and 18 of non-pulmonary tuberculosis per 100,000 members of the population. Since 1959 the incidence rate of pulmonary tuberculosis has fallen, so that in 1963 it was 95·7 per 100,000 and the mortality had fallen in the same year to 6·4 per cent. Unfortunately it is not possible to say that the same has happened with non-pulmonary tuberculosis. It is no doubt common knowledge that much of the improvement in the outlook for this disease has been the result of the introduction of potent chemotherapeutic drugs, but it is perhaps not so widely appreciated that treatment with these drugs requires careful bacteriological control. Strains of the micro-organisms vary considerably in their sensitivity to the various drugs which are available and there is the further problem that during treatment, particularly if it is interrupted or

inadequate, strains may develop resistance to the particular chemotherapeutic agent which is being used. Thus, Briggs (1963) has shown that 11 per cent of patients presenting at the Infectious Diseases Hospital, Salisbury, were already resistant prior to the start of treatment and that this figure rose to 21 per cent in those under treatment. Thus a vital part of any tuberculosis control programme is the sensitivity laboratory which works hand in glove with the clinician. Here the College is particularly fortunate in the magnificent donation given by the Rhodesian Association for the Prevention of Tuberculosis to establish such a laboratory. It is my earnest hope that the bacteriologist who will be appointed to the staff of the Department will have the Mycobacteria, that is the group of organisms which includes the tubercle bacillus, as his major research interest, for there are many questions in connexion with the organism which are still unanswered, such as variations in virulence which have been observed in other countries, the true significance of the development of resistance, and the interplay of the two factors virulence and resistance (Šula, 1963).

The performance of drug sensitivity tests and the observation of resistance could be regarded as part of the routine work of the Department. There are other problems of a more theoretical nature. A close relation of the tubercle bacillus is *Mycobacterium leprae*, the causative organism of leprosy. I spoke earlier of Virchow and it is therefore interesting to note that the characteristic cell which is seen in the lesions of leprosy was discovered by Virchow in 1864 while working in Norway; furthermore, the bacillus itself was discovered by Hansen also in Norway. (This underlines the fact that the so-called tropical diseases form no natural group based on any common causation; the

organisms involved differ from one another just as much as those causing disease in temperate countries. These diseases are rife in the tropics because of environmental conditions and there are very few diseases indeed which can be regarded as truly tropical. Thus, malaria was endemic in Lincolnshire, East Anglia, and Kent until 1860; outbreaks of yellow fever have occurred on the eastern seaboard of North America as far north as Boston and there were epidemics in Spain, Portugal, and Italy up till 1878. Put in another way, the disease problems of tropical and developing countries are often separated by a difference of time rather than pattern from those of temperate and industrialized communities.) Unlike the tubercle bacillus, the leprosy bacillus has proved particularly difficult to study in the laboratory for it has not yet been possible to cultivate it on artificial media. There are many problems in relation to leprosy and its pathogenesis which still require solution. One which appeals particularly to me, as an immunologist, is the suggestion by Lumsden (1963) that much of the tissue damage in this disease may be the result of a process of autosensitization. The concept that the body's own tissue may act as potentially foreign substances, with the production of tissue damage either as a result of the formation of antibodies against those tissues or by some related mechanism, is a recent one. It has been investigated very intensively during the last few years, particularly in relation to some diseases of the thyroid gland and to such a common disease of temperate climates as rheumatoid arthritis. No clear-cut cause-and-effect relationship has been established in man between antibodies against tissue components and the production of tissue damage but the results in a number of experimental models are suggestive. One of the most extensively studied of these models depends upon the

injection of nervous tissue along with certain mycobacteria or their products. The conditions which obtain in leprosy are the closest human parallel to this experimental situation. To my knowledge Lumsden's hypothesis has not yet been put to the test. We in this country are in a good position to do so and to take up this line of investigation. Indeed, we could do no better than take heed of the statement made by Hanks (1945) who wrote, 'it seems a pity that the almost universal pre-occupation with the cultivation problem has prevented strategists in the field of leprosy from enlisting the full-time participation of professional immunologists and serologists'. It is more than ninety years now since the micro-organism was recognized and it has resisted repeated attempts by research workers to unravel many of the mysteries connected with it.

The second major field in microbiology is virology which is as yet almost completely unexplored in this country. The nearest virology laboratories at present are situated in Entebbe and in Johannesburg so that only diagnostic work is possible and any material for this purpose has to be sent enormous distances. It is, of course, true that a Pasteur Institute was set up in this country in 1902 for the investigation of rabies, several outbreaks of which occurred in the first decade of this century. The activities of the Pasteur Institute in the preparation of vaccine continued to appear in the Public Health Report for Southern Rhodesia until 1945. No outbreak of the disease was recorded between 1913 and 1945 but occasional cases have occurred nearly every year since then. Progress in virology in the last few decades has been such that there are now well over 400 antigenically distinct animal viruses known and a new type is identified almost every few weeks. Much fascinating work has been done, particularly at Entebbe, on the group

of arboviruses, that is, those viruses which are carried by arthropods. Numerous species have been discovered in Uganda and carry names which indicate the geographical source of their first identification, e.g. Semliki, Bunyamwera, and Ntaya, or of the disease for which they are responsible, such as Chikungunya or O'nyong-nyong, both of which are tribal words indicating the extremely painful manifestations which occur on infection with either of these viruses. The latter two viruses are closely related to one another, causing rather similar diseases; O'nyong-nyong was responsible for a limited outbreak in the Sabi-Lundi valleys in March 1962. This is the only known outbreak of disease caused by an arbovirus in this country; there may well have been others. Clearly there is great scope for the study of animal and human viruses of this group in relation to the fauna of forest trees in this country and of the possible interplay of virus diseases and parasitic diseases, not to mention the investigation of the outbreaks of febrile illness which cannot clearly be diagnosed as one of the known diseases within this or other groups. I regret that any attack on these problems must be delayed until such time as the Department occupies its premises on this site, for the laboratory accommodation which is available to us at Harari Hospital is quite inadequate for the setting up of a virology laboratory.

Finally I should like to say something about a relatively new concept, namely geographical pathology. The idea of associating a disease with a geographical location is not new; textbooks of medicine contain many such terms as 'Derbyshire neck', 'Bombay boil', and so on, which indicate the frequent occurrence of certain conditions in well-defined localities. Much more recent, however, is the deliberate planning of epidemiological or demographic surveys on

an international basis with the intention of eliciting common factors which may be responsible for either high or low incidences of disease in different communities. Much of this work has been done in relation to cancer but interesting information has been and is being collected about other diseases, such as malaria, diseases of the heart, tuberculosis, and peptic ulceration. The subject is considered sufficiently important in the U.S.A. that a whole division of the Armed Forces Institute of Pathology in Washington, one of the leading centres of its kind in the world, devotes one of its nine divisions entirely to geographical pathology. This Institute carries out co-operative studies with laboratories all over the world.

In Africa a serious attempt is being made to get information about the prevalence of many diseases in different communities. This survey was initiated at the Central African Radiological Congress held in Bulawayo in 1962 and has been in active progress in East Africa and in this country for about two years. The idea has been adopted in South Africa and it is hoped that it will be used in West Africa. The aim is to send or take questionnaire forms to every hospital where there is a doctor. These forms simply ask whether certain diseases are seen weekly, monthly, or less frequently or whether facilities are inadequate for a diagnosis to be made. There are, of course, weaknesses in a survey carried out on such wide terms as this. Nevertheless, information from district and mission hospitals is important and the staffs of these institutions are much too busy to be expected to spend long hours looking up records. Comparisons of the results of this type of survey with accurate hospital statistics show a surprisingly small error. The South African Institute for Medical Research has agreed to process all the information through its

cartography department which will produce maps for each disease. A survey such as this should indicate those major differences in prevalence which require further investigation as to their cause. This sort of work, which is inexpensive of apparatus or personnel, is an essential preliminary to detailed investigation of the aetiological factors of many diseases. Furthermore, a survey of this type carried out in person can lead to valuable contacts between members of the Department and the all-important doctors who are in immediate touch with the health problems of the country.

We come now to a consideration of the translation from potential to achievement. It is obvious that any research must be done within the resources of the Department, the Faculty or the Hospital in which it is hoped to pursue it. What are these resources? The establishment at which we are aiming is that suggested by the Nuffield Committee (1959), namely, seven academic staff and approximately fifteen technicians. When one considers the complexity of pathology and the expert knowledge required within the several branches of the science, this will allow for only one member of academic staff in each of the main divisions. Apart altogether from any consideration of research this is the bare minimum which will be required for the diagnostic and teaching duties of the Department. It will not be easy to find adequate time for research, but such time must be found unless stagnation is to occur. Fortunately the Nuffield Committee suggested that two registrars should be added to the academic staff; furthermore, their estimate was based on an intake of twenty-five students. If we are to maintain a satisfactory staff : student ratio these numbers will have to be increased in the next few years. Indeed there is ample precedent for giving very serious consideration to

the establishment of at least one more independent department. The subdivision of pathology into separate departments of morphological pathology and of microbiology dates from the second decade of this century when Edinburgh, in 1913, and Glasgow, in 1919, established full-time chairs in bacteriology, having had combined chairs since 1831 and 1894 respectively. Now every medical school in Britain has these two departments and a large proportion have an independent department of chemical pathology as well. This, indeed, is the pattern in many other countries, for a single department in a large medical school would be unwieldy.

There may even be those amongst you who may be questioning the wisdom of the present arrangement in the College, for it is clearly evident that no one person can acquire sufficiently detailed knowledge to be able to give expert advice in all the branches of pathology. Nevertheless, there are advantages in the present arrangement. During the early, planning stage of the medical school and its curriculum a great deal of co-ordination is required, for it is our aim so to plan the course that our students will be taught medicine as a whole rather than as a series of isolated disciplines. Each of these disciplines has a contribution to make to that whole and the principles of each should be taught separately. But the application of these principles to the study of patients should be integrated as much as possible. In their clinical years students should be taught about diseases by a multidisciplinary approach rather than learning about the morphological, microbiological, radiological, and clinical aspects of a disease at intervals of many months, as happens too often in established medical schools. There are advantages, also, on the research side. All of the lines of investigation which I have discussed, except

geographical pathology, will require the technical procedures of at least two of the major subdivisions of the subject. This will require very close co-operation between the individuals concerned if optimum use is to be made of the relatively limited time and facilities available. Clearly such co-operation can be achieved more easily in one department than in several. Furthermore, in a department which is itself almost multidisciplinary each member of the staff can make his major contribution within the field of his greatest competency while, at the same time, challenging the accuracy and significance of observations and traditional teaching in related fields of the discipline. In this way the whole can become greater that the sum of its parts. But I should not like to see these arguments used as reasons for postponing the setting up of a Department of Microbiology for eighty-two years, to take the example of Edinburgh, or even for twenty-five years, as in Glasgow.

There is another important way in which the research potential of the Department, indeed of the whole Medical School, can be enhanced. This is by the encouragement of participation by students. The authors of the second Nuffield Report took cognizance of this and discussed student participation in research problems in anatomy and physiology. Their suggestions were implemented in the Department of Anatomy during the last long vacation. We intend to provide similar facilities in the Department of Pathology, for this is an opportunity for those students whose inclination is towards an academic career to find out whether this is a serious interest. Indeed, we feel that it is sufficiently important for all students to have taken part in a research project that time will be made in the clinical years for this to be done. This is now a feature of the curriculum of many medical schools and one which, if well

planned, can be of great value both to the Departments concerned and to the individual student, whose critical faculties can be enhanced considerably during the exercise.

If I have belaboured the question of staff it is because I believe that it is a most important factor in the development of our research potential. To state the corollary that large sums of money are less critical is not to suggest for one moment that research can be done for nothing. But we must be realistic. A great deal of the medical research which is needed at the present time in this country does not require an electron microscope or an ultracentrifuge. The time will come when this sort of apparatus will be necessary but let us concentrate, for the next few years, on gathering basic information and investigating a few of the vast number of problems which can be tackled with those resources which are already available or within our foreseeable means. The potentials are great; let us apply ourselves to them with diligence and with enthusiasm.

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