WHITHER CLINICAL PATHOLOGY? TRENDS AND OPPORTUNITIES *

BY

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At the turn of the half-century, a little over a year ago, I was asked to contribute an article to the *British Medical Journal* on "Fifty Years of Clinical Pathology" as one in a series of articles on the same theme in other branches of medicine. The composition of that article was intensely interesting and highly self-educative. The study of the historical facts revealed certain milestones which themselves had given rise to trends in the subject which is our own. I have thought, therefore, that it might be of interest to try to think out what are likely to be the trends of clinical pathology in the years ahead, atomic bombs permitting, bearing in mind, first, the speed and trends of scientific advance, secondly, the impact of nationalization upon the practice of medicine, and, thirdly, what we can do to prevent the personal side of our particular craft from being submerged in the impersonality of the State.

Let us, in the first place, consider the speed of scientific advance in relation to what may be called the growing points of medicine. None can doubt that chemistry has come to be the foundation of nearly all scientific procedures, for it forms the fundamental basis of many of the laboratory manœuvres which hitherto, or until recently, we have performed by rule of thumb.

A few examples will make this concept abundantly clear.

For many decades we have used this or that medium for the cultivation of particular bacteria. These media were devised on an empirical basis—by trial and error, indeed, on much the same principles as governed therapeutics until relatively recent times. Now we appreciate that a particular medium will grow a particular organism because of the metabolic requirements of that organism, to wit, on account of the chemistry of its vital processes. Our empirical media contain this or that specific substance which is essential for the organism.

Likewise with histological staining. Whereas at one time a process of trial and error determined the best stain for a particular tissue and stains which provided the best specific contrast for this or that material, we now know that the virtues of these different stains depend upon their affinity for particular chemical groupings in the tissue itself. Cytochemistry or histochemistry is now a science of its own, and the application of a stain has as its object the demonstration of a specific chemical substance, rather than the production of a pleasant contrast histological picture.

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I have in mind such procedures as the specific stains for ribose nucleic acid and other essential substances concerned with the metabolic processes of vital cells. Such stains, for example the Feulgen-reaction, enter also into haematology, and all will be familiar with the differences between vital and post-mortem staining.

Chemistry has indeed come to loom large in our workaday lives, and, since the basis of all physiological function as well as pathological dysfunction 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. I need hardly remark how important are the accurate estimations of the chemical pathologist in carbohydrate metabolism, renal function, liver function, gastric function, fat metabolism and fat 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 with the complex problems of coagulation of the blood which involve numerous chemical procedures.

Let this then be the prime answer to the question posed in the title of my address, that the signpost for clinical pathology in the future is clearly pointing to the chemical aspect of the subject for those who wish to keep their individuality and to provide the personal opinion which has been the main aim of the clinical pathologist of the past. Nationalization, by creating regional bacteriological laboratories, may take from the clinical pathologist much, if not all, of the bacteriological work which he has performed in the past, and certainly when such work involves an epidemiological problem. Morbid histology is to a large extent an impersonal aspect of the subject. One is left with the certainty that the personal opinion of the clinical pathologist will always be needed in the fields of haematology and biochemistry. Pathology in these fields cannot be divorced from a clinical opinion, and it is upon these aspects of medicine that the budding clinical pathologist should concentrate. But if this be the prime answer to the question I have posed, what else can we do to save our souls from routine, to exercise our intelligence in relation to the numerous opportunities which are presented to us, almost daily though perhaps unnoticed, and to advance our subject so that it comes to occupy the forefront of medicine, as indeed it should, for our branch of medicine is in the British tradition, the natural gradual evolution which combines the clinical acumen of the past with the somewhat mechanical science of the present. I make no criticism of my numerous American friends when I say that many of them have tended to over-emphasize the latter, whereas many British physicians still insist upon living in the days of Sydenham and Heberden.

We have, I am sure, unrivalled opportunities for advancing the science and art of medicine, so long as we are ever alive to the significance of what we have to study and so long as we regard our work as having this potential bearing. To show what I mean, I propose to devote some time to making a number of provocative pronouncements about the nature of leukaemia—a disease in which I have been interested for a quarter of a century, a disease with whose tragedies we are all too familiar. I make these observations because it is the function of a presidential address to stimulate thought and to show what problems can be presented, even though they may not be solved, by constant pondering on the material which passes through one's hands almost daily. I do not anticipate that I shall tell you anything new, but I may be able to present to you, from another angle, the facts which you already know.

In this dread disease, leukaemia, there are numerous manifestations which are recorded as isolated facts in textbooks of medicine without any emphasis upon the conclusions which can be drawn from them and without any attempt to bring them into a perspective where they can be used to discuss the nature of the disease. The spectacular and absorbingly interesting haematological changes have received the most minute attention, and this alone has tended to overshadow the morbid anatomy and basic pathology and also to divert attention from certain clinical facts which may provide the clue to the elucidation of the cause and the devising of appropriate treatment. The development of modern methods for studying cell growth and cell metabolism—to wit, the vital chemistry of the living cell, the aspect of clinical pathology which I have emphasized as being the signpost for the future—has also thrown further light on the problem of leukaemia by revealing the nature and potentialities of the leukaemic cell which have usually been regarded as undoubtedly malignant on account of the invariable fatality of the disease and, in the clinical field, the obvious superficial resemblance to cancerous conditions.

First let me take up some points on the clinical side. All leukaemias are characterized by an abnormal proliferation of leucopoietic tissue in the bone-marrow, the proliferation being at an immature level which usually, but not always, results in the appearance of large numbers of leucocytes in the peripheral blood. Many of these are immature, and the degree of immaturity bears a rough relationship to clinical severity. The most acute types are characterized by a preponderating, if not an exclusive, presence in the blood of cells so primitive that they often defy exact differentiation. Likewise with the terminal phases of the chronic types which are often acute from both the clinical and the haematological aspects. These well-known facts should give food for thought.

In malignant disease in general we recognize acute fulminating growths such as the mesoblastic sarcomata, and at the other end of the scale the chronic, long-standing scirrhus types of carcinoma. This then is common ground with leukaemia. But it is difficult to think of examples of orthodox malignant disease in which the chronic scirrhus type suddenly and terminally takes on a fulminating character. We know also that leukaemia may remit spontaneously, or from the intrusion of other complications, or as the result of treatment. But in other malignant disease spontaneous remission is so rare that when it occurs it raises grave doubts as to the accuracy of the original diagnosis. Thus, there are certain clinical features of leukaemia which seem to separate it from orthodox malignant disease. However, there are certain features common to both, for example, the progressive anaemia, the associated cachexia, and the invariable fatality.

Let us now take up a haematological point. We are thoroughly familiar with two types of the disease which we designate as leukaemic or aleukaemic, according to the state of the peripheral blood, but these do not differ greatly in clinical features save that in aleukaemic cases the lymph nodes, the spleen, and the liver may not be so grossly enlarged at the outset. This fact, that the disease may be leukaemic or aleukaemic, is accepted as a commonplace, a mere variation in manifestations. It has not given rise to argument and serious discussion. Yet the fact that two types exist suggests the derangement of two different processes which, on rational grounds, should be physiologically interlocked. I refer, of course, first to the process of maturation and, secondly, to the process of release into the circulation. We are

woefully ignorant of the nature of any materials which we could confidently call specific maturation factors, factors, say, which cause the myeloblast to mature to the granulocyte, and we know even less of the forces or factors which regulate the release of granulocytes into the circulation or which restrain the myeloblast from so doing. Thus, in frank leukaemia, there appears to be inhibition or retardation of maturation in whole or in part, combined with lack of control over release, since vast numbers of cells, including primitive ones, flood the circulation.

In the aleukaemic disease, on the other hand, lack of maturation is a prominent feature, but the release mechanism is largely intact in that the numerous primitive cells in the marrow may not reach the circulation except in small numbers.

These facts make it abundantly clear that we know little or nothing of the physiology of leucopoiesis, and I am convinced that we shall not understand leukaemia until some of these basic physiological facts have been determined. If half the time and energy which have been devoted to devising and exploiting empirical remedies for the symptomatic treatment of the disease, reducing the leucocyte count, had been expended on basic physiology and pathology, we might well be much nearer to rational treatment.

I may mention in passing that sternal puncture has revealed how much more common is the disease than was at one time supposed. There has been a parallel decline in the number of cases diagnosed as aplastic anaemia which, in a primary form, must now be considered to be extremely rare. Many cases of aleukaemic leukaemia were previously misdiagnosed as aplastic anaemia. Even so, this is not sufficient to account for the remarkable increase in the incidence of leukaemia during the past 25 years, as shown by published statistical studies as well as the experience of most of us in practice. Even more remarkable has been the increase in the monocytic types, especially the Naegeli form. No one has yet suggested an explanation.

Let me now comment on one or two points of factual pathology and morbid anatomy which again are well known, but which are accepted as dull and ordinary and so have not given rise to the discussion which they merit.

With the fully developed leukaemic process all tissues of the body may be infiltrated with leucocytes, and in some sites these may undergo proliferation. It is this feature which gives rise to the protean clinical manifestations of the disease, so that a leukaemic patient may present at almost any of the special departments of a large hospital. I need hardly elaborate this point. Sufficient to say that the leukaemic infiltration may be gross, giving rise to pressure or derangement symptoms, or may be moderate or may be so slight, in some aleukaemic states, that even pathologists argue about the diagnosis. I would remind you too that the leukaemic cells have a characteristic distribution in the liver according to the type of the disease. We recognize the portal distribution in lymphatic leukaemia, the intercellular and intrasinusoidal distribution in the myeloid type, and the subcapsular collections in the monocytic form. In no other malignant disease in which the malignant cells are distributed by the blood stream does this peculiarly constant deposition occur.

Furthermore, as an additional argument against the malignant nature of the cells themselves, one must acknowledge that the infiltrating cells do not multiply freely, nor do they invade and destroy surrounding tissue, nor do they give rise to

a stromal reaction. The leukaemic cells may multiply in certain sites, but the nature of the multiplication suggests a comfortable symbiosis, rather than a malignant invasion, and the sites in which this multiplication most freely occurs are in the organs in which foetal blood production occurs, the spleen, the liver, and the kidney, organs in which sinusoidal spaces are abundant.

Yet, on the other hand, the rule about lack of invasive and destructive qualities is not absolute. The rare chloromatous tumour invades and destroys whilst the lymphosarcomatous tumour, the cells of which are histologically indistinguishable from the cells of lymphatic leukaemia, and which itself sometimes terminates with the blood picture of lymphatic leukaemia, both destroys tissue and gives rise to invasive and destructive metastases.

So far, I have dealt with nothing abstruse or experimental, but have merely commented upon known facts which we who see both sides of the case, the clinical and the pathological, have ample opportunity to observe, ponder upon, and correlate.

I want now to mention one or two experimental points which have arisen from these thoughts and which have been carried out by a young research student working in my department in the fields of tissue culture and cytochemistry, the results of which were communicated by him to the last International Congress of Haematology.¹

It has long been known that leukaemic cells develop into normal cells when cultured *in vitro*, but a further interesting fact is that they proliferate at the same rate as normal cells. Furthermore, tissue culture results show quite readily that primitive cells which in the *in vivo* conditions within the body of a leukaemic patient are unable to mature, nevertheless do so quite readily *in vitro*. And, finally, when such leukaemic cells are examined *in vitro* they present several points of interest. Myeloblasts may mature into granulocytes. On the other hand, if the culture be contaminated with some innocuous bacterium the cells differentiate into macrophages which ingest the bacteria. No one can quote me an example of an orthodox malignant cell which retains its capacity for differentiating into a highly specialized type of non-malignant cell given the appropriate stimulus.

This kind of result suggests that the fundamental defect in leukaemia does not lie with the cells themselves which, given an altered environment, display all the properties of normal cells in respect of maturation, rate of proliferation and, above all, a capacity to differentiate in response to appropriate stimuli. What then can we learn about the leukaemic environment? Here again we can obtain hints from the experimental field, from clinical observations, and from straightforward post-mortem examination. In the experimental field one can observe the effect of normal cells when implanted into a leukaemic subject. We are all familiar with the leukaemic nodule in the skin which is sometimes a prominent feature in an individual case. A leukaemic nodule can readily be produced in the skin of a leukaemic patient by the subcutaneous injection of a small quantity of normal marrow; the normal cells proliferate and undergo mitosis. If, however, leukaemic marrow be implanted beneath the skin of a non-leukaemic person no nodule is formed.¹ From this one can deduce that normal cells placed in a leukaemic environment behave like leukaemic cells, whilst the reverse is also true.

¹ Hoogstraten, J. (1950). Proceedings of the Third International Congress of Haematology. Grune and Stratton, New York.

Turning now to the clinical field, we know that leukaemic blood has several times been transfused in considerable volume, either by accident, or by design, in cases of agranulocytosis. But in no case has the disease become implanted in the recipient, whilst the transfused leukaemic cells have behaved as normal cells. Yet how easily do orthodox malignant cells become implanted in the site of an excision. From the clinical field also I think of what is well known to those of us who see many cases of leukaemia, namely, the intrusion of an acute infective stimulus, such as a carbuncle, which may cause a rapid and dramatic remission in a case of myeloid leukaemia. The sudden application of a dominating stimulus, an infection, may immediately cause the marrow to revert to normal. This never occurs in malignant disease. Likewise, with spontaneous remissions which all must acknowledge as a clinical fact. What has happened in such cases? It must be that the environment has altered, that whatever metabolic fault or deficiency is responsible for the disease, has shown a flicker of return to normality.

We should also take note of the clinico-pathological fact that when leukaemia is manifested it appears to arise in all places at once. So far as I know, there has been no record in all the hundreds of thousands of necropsies which have been performed of the finding of a local leukaemic marrow lesion suggestive of the inception of the disease. When the disease occurs the sinister hyperplasia is orderly, uniform, and progresses along the lines of physiological expansion as with infection, though at a more primitive level.

Ordinary malignant disease, on the other hand, begins as a local tumour which afterwards disseminates. It is, indeed, a striking fact that in leukaemia there is no question of local growth. Whatever bone is examined shows that the leukaemic process arises simultaneously in all, and this is a pathological fact which is surely unique so far as malignant conditions are concerned. It is highly suggestive that leukaemia arises from a somatic or metabolic environmental fault.

Now let me turn to the treatment of leukaemia and make certain deductions, criticisms, and suggestions from this aspect of the disease. In the first place, I have already drawn your attention to the fundamental difference between aleukaemic leukaemia, when the mechanism of maturation is disturbed but not the release mechanism, and frank leukaemia when both processes are involved. When the release mechanism is intact we are often unable to use some of our empirical remedies, such as *x* rays, urethane, nitrogen mustards, or the pterins. But when the release mechanism is disturbed in frank leukaemia then we get a form of the disease which is very amenable to anti-mitotic empirical remedies. There is therefore more than an academic difference between leukaemic and aleukaemic leukaemia. Let me next remind you of a modern rediscovered fact, namely, the, alas, only temporary effect of a massive transfusion of normal blood to the acute leukaemic case, which, *per se*, has generally been regarded as rampantly fatal. The same results, in my own experience, can be achieved with a massive transfusion of fresh plasma, though not with the reconstituted dried product. Is there therefore some inhibiting factor in the blood of all of us which prevents the development of leukaemia or does leukaemic blood lack some factor without which this dread disease develops? Is the disease therefore no more than an exhausting impotent hyperplasia, rather than a true malignant process? If this last be true, then the principles of modern treatment, which are designed to inhibit mitosis rather than remedy a deficiency,

must be fundamentally wrong. Here also in this temporary response to transfusion is another divergence from orthodox malignant disease, for cancerous processes do not remit after simple transfusion. Here too is the germ of hope for the future. For if this relatively natural and exceedingly conservative form of treatment can induce a remission, what is it that is contained in normal blood which brings about this sudden change—a change so remarkable that even the marrow may revert almost to normal. Could this factor in normal blood be positively identified we should be on the threshold, if not within the door, of a method of treatment far more realistic and rational than antimitotic measures such as assaults with such substances as variants of mustard gas or x rays which, indeed, seem to be mainly aimed at a symptom rather than at a cause.

Indeed, with new and empirical remedies we should always bear in mind that the mere reduction of a leucocyte count is no more than symptomatic treatment which may neither induce a clinical remission nor really get at the fundamental cause of the disease. We do not put out a fire by devising methods for abolishing the smoke; we do not cure an infection by abolishing the associated fever, and we shall not cure leukaemia by abolishing mitosis. The problem is really to find the something which controls and regulates mitosis, and this returns the matter to the field of chemistry which I have suggested is the main route which our subject will travel in the years to come. To my mind, the significant pointers in the field of treatment are the action, though far from satisfactory, of the pterins, and of blood transfusion; the newer knowledge that leukaemic cells contain only 10% of the normal amount of zinc and the effect, in some cases, of adrenocorticotrophic hormone. These seem to me to offer more hope of extension and exploitation than the building of bigger and more powerful death-dealing machines of highly penetrating types, since they provide a more physiological approach and even give a hint that leukaemia may eventually be categorized among the deficiency diseases in company with pernicious anaemia and diabetes.

I will admit that I am open to criticism for departing a long way from the title of my address and for having virtually stolen an opportunity to talk almost exclusively on one single subject. I have done so deliberately, for the main substance of my address is given as an example of the opportunities that come the way of the clinical pathologist. Many of you could have given other examples in relation to the diseases in which you have had a lifelong interest, and indeed I myself might have chosen several other examples and dealt with them in less detail.

Whither clinical pathology? I can say quite definitely that the subject will go in the direction in which we make it go, and the opportunities for advancing the subject of medicine are more ready to the hand of the clinical pathologist than to any other section of the profession.

I commend these thoughts to you for your earnest consideration. Those of us who are elderly would be well advised to interest ourselves in the elements of organic chemistry which we have long ago forgotten. Those of us who are still in their prime should have no difficulty in addressing themselves to this task. Those of us who are young and those who are about to enter the field of practice as clinical pathologists cannot avoid the issue. The one essential in clinical pathology is to be one jump ahead of the times, and to me it seems obvious that the future

of successful diagnosis and therapeutics lies in the field of biochemistry with biochemical control of such therapeutic agents as are found to have a specific effect in individual diseases. This is already the case with pernicious anaemia, diabetes, and other metabolic diseases. I anticipate that it will be the case with diseases amenable to A.C.T.H., and whatever materials of like nature may be discovered, and, who knows, even with leukaemia or with cancer and comparable processes which are nowadays considered to be malignant.

The future of our subject lies with ourselves, and we must never allow it to degenerate to the mechanical level of a technique. Our success in the past has been due to the individual and personal factor, to our ability to give a clinical as well as a pathological opinion. Clinical work is essentially personal. The pathological aspect must be the same. This indeed is one of the danger points arising from nationalization. For though there are still many people who will pay a private fee for a single clinical opinion, there are none, or almost none, who will pay for the host of pathological and other examinations which are ordered as the result of such a consultation. Our laboratories are therefore in danger of being overwhelmed with routine work, much of it unintelligently demanded, and with such an overburden the personal element disappears, to the detriment of original work, proper thought, and also status. It is vital that this should not happen if the craft of clinical pathology is to survive or is to make its contributions to medicine or to maintain the status which it has laboriously built up in the past 25 years. The only remedy is an increase in the establishment of fully qualified graduate staff, so that there are sufficient for each and every specimen to be the personal responsibility of the pathologist and there is sufficient time for a man to give thought to his problems. In my time I have been guilty of signing many reports on specimens which I have never seen or never questioned. I have been fortunate in having a reliable technical staff who would always refer a doubtful report. Nevertheless, I have occasionally endured the humility of having missed a difficult haematological diagnosis from lack of personal supervision, and I am sure that it is this kind of danger which nationalization threatens. In brief, it is of little use for us to clamour for specialist status with merit award if we do not personally justify that status and the award both in our everyday work and in our contributions to the advance of knowledge derived from the material which we handle.

Let us not leave our work to technicians and registrars, let us keep the personal element alive, the clinical opinion and the intelligent application of laboratory procedures to the understanding of the individual case; to wit, a modern physician. If this is done the Association will have strong and natural links with its legitimate parent—the Royal College of Physicians—and the subject will go from strength to strength in the fabric of the now irreversible nationalized service.