**An introductory address in pathology : delivered at Queen's College, Birmingham / by Gilbert Barling.**

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AN

# INTRODUCTORY ADDRESS

IN

# PATHOLOGY.

DELIVERED AT QUEEN'S COLLEGE, BIRMINGHAM,

BY

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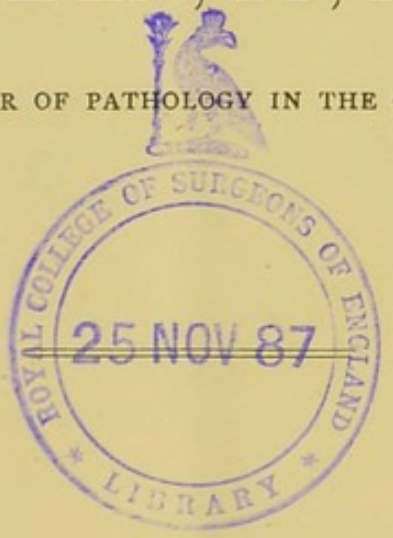


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# AN INTRODUCTORY ADDRESS IN PATHOLOGY.

GENTLEMEN,

It will not be inappropriate if I take this opportunity of thanking the Council for electing me Professor of Pathology in this College, and for the excellent provision they have made in the Pathological Laboratory for carrying on the practical part of my teaching, the more so as the latter is a recognition of the increasing requirements for Pathological study in the Medical Curriculum.

The importance of Pathological work in the *post mortem* room, in the museum and in the laboratory, both to students and to their teachers, it is not necessary for me to urge. Each of these fields of observation has its advantages, but to students particularly I would commend diligent study of the contents of the museum as a source where they may draw not only pathological knowledge, but where they may often interpret clinical teaching, for here is the ground where pathological and clinical work meet most closely. I say this not to the disparagement of *post mortem* room attendance, where many diseased conditions must be observed if they are to be seen at all, but because in the museum, specimens are always at hand for study, and they can there be found illustrating the same disease from different aspects, and affording comparison with similar and dissimilar conditions, the whole forming the most complete study of diseased tissues we can offer. I have ventured to make these few remarks because I have found gentlemen rather apt to ignore museum work

until such time as the approach of final examinations, when they become quite voracious in their demands for surgical and sometimes for medical pickles, but I know that not only are they at a disadvantage before their adversary, the examiner, but also in their future practice, owing to the neglect of the opportunity of learning which the museum affords.

Casting about for a subject to bring under your notice to-day I was embarrassed not by the paucity but by the multiplicity of subjects offering themselves, and by the difficulty of dealing with any of them in a manner worthy of your attention. Eventually, however, I decided to bring under your attention the importance of recent investigations, notably those by Sutton and Metschnikoff, on some of the physiological processes occurring in the invertebrates and in the lower vertebrates. These investigations promise to have considerable influence on our views of some pathological changes. Their tendency is to show that the phenomena of inflammation are in direct continuity with those physiological functions which provide nutrition for the organism and protect it against harmful attacks from within or without. It seems not improbable, too, that the inflammations will in future be more closely linked to that group of diseases known as the infective granulomata, and this group yet again to the sarcomas, a result much to be desired if it can be rightly attained, in that a harmonious and connected view of morbid changes will be substituted for the disjointed and abrupt notions now in existence. The investigations referred to I must recite briefly, as the time at my disposal is limited.

More than twenty years ago Haeckel shewed that if certain invertebrates were injected with indigo, amæboid cells took up the particles of pigment into their interiors, and in more recent years the same ingestion has been

shewn to take place in vertebrates. An advance upon this was the demonstration that the amæboid cells were capable of taking up not only such things as pigments, but albuminoid bodies, such as human blood corpuscles, spermatozoa, and eggs from other invertebrates and digesting them. Their physiological functions do not stop here either; but it has been shewn by Metschnikoff and confirmed by Sutton that in the development passed through by certain of the vertebrates, notably in the tadpole, parts like the tail, which disappear, are really eaten up piece-meal by amæboid cells, which can be observed attacking the tissues of the superfluous part and removing bits of muscle, nerve, etc., in their interiors. A further office is also performed by the same cells in attacking irritating substances, such as bits of glass and dust, and more important still, bacteria. When any of these are introduced into the body of one of the lower forms of life, there is an accumulation of amæboid cells in the immediate neighbourhood of the foreign substance. Material such as glass, which is not susceptible to the digestive power of leucocytes, is simply surrounded by them, the leucocytes generally remaining quite distinct but sometimes fusing together to form plasmodia or giant cells. Metschnikoff describes the process in Phyllirhöe thus: "the small granules of solid carmine were all eaten by the small amæboid cells, the larger masses were on the other hand surrounded by a plasmodium of small cells, which came one by one to each lump and flattened themselves upon it, fusing with neighbouring cells as they arrived. In this way arose plasmodia of very different sizes, which may be compared to the giant cells so often described in vertebrates," and, he continues, "in all cases in which I have found giant cells in invertebrates, they have arisen round foreign bodies and always by the fusion of separate cells."

The same observer describes a similar process in an Asterigera into which a drop of human blood had been injected, most of the corpuscles were ingested by one or two separate cells, but the larger clots were surrounded by several cells which fused to form plasmodia.

The behaviour of these leucocytes or amæboid cells towards bacteria is of the most extreme interest—"if," says Metschnikoff, "fluids containing bacteria be injected beneath the skin of Bipinnaria, or if they arise spontaneously in the wounds of such animals, they will soon be found within the substance of many amæboid mesoderm cells, both still and motile forms being ingested, individual bacteria being often seen which retain their power of movement even after ingestion, while in other cases motility is lost at once, and the whole bacterium becomes so delicate as to be scarcely visible, and experiments on Botryllus, shewed not only a passive ingestion of bacteria but an active pursuit of them by the amæboid cells and their ingestion and absorption, but," says the author rather pathetically "the victory was not however all on one side, here and there were found mesoderm cells, to all appearance dead, with long bacterial filaments projecting from them."

In another paper the same writer describes similar occurrences in a frog, beneath the skin of which putrescent blood had been injected, bacteria both still and motile were found within the white blood corpuscles. Summing up these observations it is clear that the amæboid or mesoderm cells of invertebrates and the lower vertebrates, in addition to their nutrient functions, have also the power of digesting soluble bodies, such as human blood corpuscles, of destroying bacteria by ingesting them, and of removing parts of the body that have become superfluous. These digesting cells represent principally

leucocytes or white blood corpuscles, but also to a limited, extent the fixed connective tissue cells which, under certain conditions, assume amæboid movements ; beyond this it is found that giant cells are formed by the fusion of leucocytes, and generally with the purpose of overcoming some foreign body with which a single cell is not able to cope.

Careful study of the facts above recited shows how close is the analogy between these digestive and destructive processes, most of which are truly physiological, and those which we regard as pathological and describe as inflammatory.

Inflammations may be divided according to their causation into two classes, the localised and the spreading, the former being produced by the contact of bodies such as aseptic sponge or glass with the tissues, or by extravasation of blood into the parts around vessels, but not communicating with the air, or by such injury as is produced by an actual cautery on the centre of a muscle, in all these cases the effect of the injury is limited to the area first damaged. The spreading inflammations on the contrary are due to the presence of micro-organisms ; they are not circumscribed to the area at first receiving the germs, and many of them have the power of inducing secondary inflammations in other parts of the body, and hence are spoken of as infective. Whatever may be the causes the effects are similar, though varying in degree, and those effects which constitute the essence of inflammation are the escape of leucocytes from the blood vessels into and around the injured area with a varying amount, according to the chronicity of the attack, of proliferation of the cells normally forming part of the tissue, but always the leucocyte is the predominating factor.

Typical of the cause and consecutive inflammation first referred to as the localised, we may take the results produced by a hæmorrhage into the brain, or by the introduction of bodies such as aseptic decalcified sponge, or a bullet into the tissues, with proper precautions to exclude micro-organisms. Whether a foreign body be introduced from without, or whether it be provided by a hæmorrhage from within, which is practically the same thing, as the extravasated blood is to all intents and purposes a dead, and therefore, a foreign substance, the characteristic leucocytic escape takes place into the surrounding tissues, and, if it be possible, as it is in the case of sponge or blood clot, into the substance of the foreign body itself, the initiator of the whole change; examination of the intruded material at a later date shews various stages of development of the leucocytes into fibro-blasts and giant cells with an active absorption, especially on the part of the giant cells, of the sponge filaments, and eventually the sponge disappears and we find no trace of its structure. The giant cells are similar to those found in absorbing bone and known as osteo-clasts, and resemble sometimes the giant cells of tubercle in the peripheral arrangement of their neuclei, though that is not constant, as the neuclei may be scattered and arranged in an irregular manner as in the myeloid cells of sarcoma.

Extravasation of blood, as in a cerebral hæmorrhage, excites similar changes, and the blood and degenerating tissue around share the same fate as the sponge; in the lymph spaces around the vessels corpuscles can be seen laden with fragments of degenerating cells and blood pigments, some of which can be recognised in the glands into which the lymphatics of the part empty. If the foreign body introduced be incapable of solution, a bullet for instance, the energy of the leucocytes which surround

it seem to be directed to circumscribing it from its host, a barrier of fibrous tissue develops round the intruder, and we say it has become encapsuled.

The spreading inflammations are generally, if not always, dependent upon bacteria for their origin, doubtless the micro-organism being often grafted on to the localised inflammation and changing its character. Here again the presence of the foreign substance is followed by that emigration and infiltration of leucocytes into the injured part which we recognise as a necessary part of inflammation, some of the leucocytes remain as pus, others develope into fibres and form a barrier between the pus and adjacent tissues (constituting what we recognise as an abscess sac), and yet others return into the lymph stream. It is not justifiable to make any positive statements as to the relations of the leucocytes and the invading bacteria, but judging from what has been described of the actual ingestion of bacteria by the amæboid cells of botryllus and of the frog, and from the demonstration of the presence of the bacilli of anthrax, and of mouse-septicæmia in white blood corpuscles, and yet again of the presence of tubercle bacilli in the cells found in that disease, it does seem most probable that the object of the leucocyte is to enclose and destroy the micro-organism, although sometimes falling a victim itself to the action either of the bacterium or of some poisonous chemical product of the latter, and the presence of pus corpuscles may be explained possibly by the destruction of leucocytes by this poison.

Such, then, is the evidence that inflammation is in direct continuity with physiological function; passing beyond the ordinary limits of the latter in health, because an increased effort is necessary to protect the organism against something that is inimical to it, inflammation

being the expression of that effort, which is the more severe and intense as the intruder is more hurtful to its host. If this be so, we must be careful to discriminate between inflammation and its causes, the former being in reality a conservative process, and to be welcomed as the effort of nature at self cure ; but whilst our prejudices against the results may be modified, against the causes they will be increased, and pro-phylactic measures be rendered more urgent.

The second division of the inflammations, characterised as the spreading, is also spoken of as infective ; that is capable of inoculation from one host to another, and often of giving rise to secondary centres of inflammation which originate from the primary lesion. In this way the spreading inflammations are connected very intimately with that group of diseases, the infective granulomata, which includes tuberculosis, leprosy, glanders, and a few others. It is not necessary to go into details of all of these, but I will bring under your notice two of them which may be regarded as typical of their kind, viz., tubercle and actinomycosis. In tubercle, bacilli, supposed to be characteristic of that disease, are found amongst a collection of cells of varying characters, some of them small, round, and nucleated, like the leucocytes of inflammation, others of larger size, and known by the unfortunate name of epithelioid, but much better as fibro-blasts, and generally one or more giant cells, the last two forms at one time regarded as essential parts of a tubercle, and as characteristic of it, though no longer so esteemed. These various cells are similar to those found in inflamed tissues, those at the edge of the tubercle resemble the white corpuscles of the blood, which by their growth, sometimes assisted by proliferation of the connective

tissue cells of the part, produce the epithelioid cells or fibro-blasts; and again, by aggregation and merging of these cells, or possibly by imperfect segmentation, giant cells are formed. In addition to these cellular elements, there is present a micro-organism, classed as a bacillus; this bacillus is found constantly in that disease which is clinically recognised as tuberculosis. From the tubercle it can be separated and cultivated in suitable sterile nutrient media, at a temperature about that of the body heat, producing a characteristic growth both to the naked eye and under low magnifying powers. The cultivated bacilli can be inoculated into animals with the resulting production of tuberculosis; and finally, in the tubercle thus artificially produced, bacilli, similar to those commenced with can be found. This one may say is as perfect a demonstration as it is possible to have of cause and effect, and which we owe to the splendid researches of Koch; the intrusion of the micro-organism is resented by its host, and that resentment is expressed by a cellular hyperplasia wherever the bacilli may be lodged, the resulting collection is developed from the same elements as the ordinary inflammatory formations, and is indistinguishable from them in the character of the cells found. Seeing then that we regard other micro-organisms as efficient causes of inflammation, and that we are unable to differentiate between the cellular hyperplasia of tubercle and that of inflammation, I do not see how tubercle can be divorced from the true inflammations.

The other infective granuloma I have selected, Actinomycosis, is a disease much more prevalent in cattle than in man. Its favourite sites in animals are the jaws, especially the lower, where it produces tumors of considerable size, even as large as a child's head, which on section shew a greyish white juicy surface with

a spongy structure, and present at intervals yellowish points resembling small abscesses. It is interesting to note that these tumors are often spoken of by veterinarians as sarcomas and osteo-sarcomas. Microscopic examination shews that the patches looking like small abscesses are in reality fungus growths arranged in a star-like form (hence the name of actinomycosis or star fungus), and that the bulk of tumor consists of granulation tissue resembling that of ordinary inflammation. If a small nodule be examined, in its centre will be found the ray fungus surrounded by numerous fibro-blasts and by some giant cells; further from the centre are small round cells, and external to these a zone of fibrous tissue forming a kind of barrier between the nodule and the surrounding parts. (Woodhead and Hare. Journal of Anatomy and Physiology, Vol. XX).

The likeness of this granulation tissue to that of ordinary inflammation is exact and its sources similar, viz., the white corpuscles of the blood and probably the fixed connective tissue cells of the part to a small degree. In animals the fungus may be present in the glands of the mouth and tonsils, and remain there innocuous until some abrasion admits them to the lymphatics, when actinomycosis is produced, and this may act as a centre from which secondary infection of other parts of the body may take place. The disease is inoculable from cattle to cattle and from man to animals, and it is possible also to cultivate the ray fungus in nutrient media. In the few cases that have been described in the human subject, it appears that the favourite site for the nodules is in the jaws or their neighbourhood, where they may remain localised, or else be disseminated through the lungs, spleen, liver, and bones, especially the vertebræ. Appearing first as an infiltration the nodule

becomes circumscribed and dense, then softens, and finally, if not opened by the surgeon, discharges a purulent fluid which contains the fungus.

To sum up these remarks on actinomycosis we have a disease in man and animals dependent on the presence of the ray fungus, capable of inoculation from one host to another, producing a cellular hyperplasia such as is characteristic of inflammation, forming nodules or tumors which in animals may be of considerable size, but in man seem to have more tendency to suppurate, in either subject, however, giving rise at times to infection of distant parts. It is, therefore, doubtful whether it is desirable to retain the term infective granulomata, and whether, at all events as far as tubercle and actinomycosis are concerned, it would not be better to speak of them as infective inflammations due to specific causes, in the one case to the tubercle bacillus, in the other to the ray fungus, and it appears as though the inflammatory processes here have the same intention as the simpler and ordinary inflammations, that is the limitation and destruction of the exciting cause.

The ground upon which I am now about to venture, in examining if there be any relationship between the conditions I have just discussed and the malignant growths, is much more difficult, the gap between them not yet to be completely bridged over; still there are some points worthy of consideration, especially in the relations of that class of malignant growths known as the sarcomas, to which my remarks will be principally limited. Sarcomas may be defined as tumors consisting of connective tissue in an embryonic condition, with a tendency to indefinite increase in size, and with the power of producing secondary tumors in other parts of the body. Microscopic examination shews cells varying

considerably in size, shape, and general arrangements, but all of them having their counterparts in the various stages of development of the cells of inflammatory formations into adult connective tissue, indeed so like are the cells in the two cases, round, spindle, and giant or myeloid, that without knowledge of the site and clinical history of the tissue under examination, it may be impossible to decide microscopically whether the new formation be part of a sarcomatous growth or a product of inflammation; the development of new vessels and the relations of the cells to those vessels assists in making the likeness more complete. If the edge of a rapidly growing sarcoma be examined its method of increase may be followed and it will be found to occur in two ways; first, in importance, according to Cornil and Ranvier, is the increase by proliferation of the sarcoma cells already existing, and they describe and figure this proliferation as commencing in changes in the nucleus, eventuating in its dividing into two, this being followed in turn by division of the cell protaplasm.

The second method is independent of the sarcoma cells and comprises two plans probably, one, by proliferation of the normal connective tissue cells of the part, the other by migrated leucocytes at the edge of the tumor; from both these sources small round cells are produced which can be followed, increasing in size, and varying in the relations of cell protoplasm and nucleus, until they resemble the original sarcoma cells which they have reinforced. Now I need hardly remind you that the increase of inflammatory cellular collections is repeated in the sarcomas, the fibro-blasts of inflammation increase by sub-division, and they are added to by proliferation of fixed connective tissue cells, and by emigration of leucocytes, so that sarcomas are connected to inflammatory

hyperplasia, not only histologically but also genetically.

There is one form of cell frequently found in sarcomas to which I think more importance attaches than is generally believed; it is, I think, specially significant in a chain of relationship such as I am suggesting for your consideration; that cell is the giant cell. A component to a small degree of many sarcomas, it reaches its maximum in those tumors which are known as myeloid. Unfortunately not frequent, these tumors have much importance attached to them, from the fact that surgeons are able to give a much better prognosis after their removal than after that of any other tumor of the sarcomatous group, because, once completely removed they have little tendency to return, and rarely give rise to secondary deposits. But to justify the application of the term myeloid to any particular sarcoma, Mr. Butlin has pointed out that the giant cell must not only be present but it must be predominant in numbers, or perhaps it would be equally correct to say that a good prognosis may be given in a sarcoma in proportion to the number of giant cells found in it. These remarkable bodies exist as natural constituents of the medulla of bone, they are formed as the result of irritation by such substances as cause inflammation, they are found in the hard chancre of syphilis, and in the nodules of tubercle, and are always characterised by the presence of numerous nuclei of considerable size and generally oval in shape, imbedded in a mass of protoplasm of variable size and form, in which the nuclei may be arranged in an irregular manner, or as is commonly the case in the giant cells of tubercle, like a fringe at the edge of the mass, and occasionally the protoplasm has fine off-shoots connecting it with adjacent fibres or cells.

Now the purpose of giant cells in bone, and in the

inflammatory neoplasia, appears frequently to be that of absorption; they are either removing parts no longer useful, as in developing bone, or some irritant to the tissues, as in the case of sponge grafts, and it will be in your memories that the plasmodia or giant cells of invertebrates were concerned in surrounding and probably digesting particles of pigment or foreign substances like injected blood; and again in tubercle the bacilli found in that disease are to be seen in large numbers in the interiors of giant cells. So it appears as if there were a definite reason for the existence of these cells, their function being to offer a more active opposition to, or to destroy, dead or invading substances, whether bone, sponge, blood, or micro-organism. Remembering then that giant cells are associated with diminished malignancy in sarcomas, is it an unfair inference that here as elsewhere they represent an increased effort, and a successful one too, on the part of the tissues to destroy something which is injurious to them, and which is the actual cause of sarcoma. The giant cells are not to be seen consuming adjacent structures, as in bone or sponge absorption, but they appear quiescent, as do those of tubercle. Whether eventually myeloid cells of sarcomas will be found to have a definite relationship to micro-organisms, such as is seen in the giant cell of tubercle, I should not like to prophecy, but I must say my expectation is that the explanation of the malignancy of sarcomas will be found in that direction. The mysterious characters summed up as malignant still elude our attempts at unravelling them. We know no better now than formerly whether to blame the cells of the growth, the constitutional tendencies of the patient, or some parasite; but one cannot help feeling that the recent investigations of tubercle, itself often formerly regarded

as a malignant growth, justify the hope that we are approaching a solution of this difficult problem.

The origin of tumors, always a favourite topic for pathologists, received additional interest from a theory suggested by Cohnheim, which supposes that certain cells of the fœtus remain undeveloped, it may be for years, in the midst of normally formed tissues,—in fact that there is a latent embryonic rudiment from which at any time a tumor may be developed, the impulse which starts it being sometimes a definite injury, at other times undiscoverable. Considerable force is given to this theory, so far as innocent tumors are concerned, by the formation of enchondromata of bone, which originate in islets of cartilage left unossified in the centre of the bone from which the tumor arises, and in the development of tumors from pre-existing structures left unutilised in fœtal life, such as were so ably treated of by Mr. Sutton recently, at the College of Surgeons; but a pure enchondroma is a perfectly innocent tumor, as are all the teratoid tumors, and in neither case do we get recurrence or secondary infection if the primary tumor be removed. Experiments made on transplantation of fœtal tissues into animals whilst giving some support to Cohnheim's theory, as far as the production of innocent tumors is concerned, lend no support to the idea that malignant growths arise in the same way. It has been found possible to transplant bits of fœtal cartilage into the peritoneal cavities and eyes of rabbits, where they survived and grew for a time, but the development was feeble and lent no support to the supposition that from these fœtal elements malignant tumours could originate. If it were found that sarcomas increased only by multiplication of their own elements, their origin from latent fœtal rudiments would be more probable, but we know that many of the cells of these

tumors are derived from proliferated connective tissue cells or from leucocytes.

There are two chief lines along which the enquiry may be pursued as to the existence of any relationship between the malignant growths and the infective granulomata. The first relates to the characters of the cells, their origin and increase. So far as I am able to day, I have pointed out to you those points that appear to be of importance under that heading, and I have left for consideration the question of infectivity, that is, whether it is possible to produce malignant growths by inoculation from one animal to another. Such attempts up to the present time appear to have failed, but possibly, as Mr. Savory suggested in his Bradshaw lecture, because of the unsuitable conditions under which they were performed ; and he further points out that clinical observation occasionally offers what appears to be an illustration of this inoculation, when the surface of a cancer coming in contact with an apparently healthy surface, sets up malignant growth in the formerly healthy part. This is occasionally seen in the mouth, where a tumor of the gums, or from one of the jaws, coming in contact with an opposed healthy mucous surface of the cheek, sets up growth there.

Mr. Butlin has pointed out in his work on Sarcoma and Carcinoma, that some epitheliomas of the esophagus invade the trachea and eventually ulcerate into its channel, and he specially refers to three of these in which secondary growths appear to have been set up in the lung by fragments of the epithelioma carried into the terminations of the bronchi by the inspired air, and Dr. Moxon also supports that theory in one of his cases referred to by Butlin. If these observers are correct in their surmise, some support is certainly afforded to the belief that auto-inoculation may be effected.

I saw recently an autopsy which suggests the possibility of this direct contagion of malignant growth in the case of sarcoma. The subject had suffered from sarcoma of the omentum, and the *post mortem* revealed a number of small nodules of growth in the peritoneum immediately around the growth and in the pelvic peritoneal pouches, especially in the latter, where the nodules were crowded as thickly as they could stick. The upper parts of the serous membrane were not affected by the nodules. I am inclined to believe that these nodules were transplanted directly without transference by either blood or lymph stream; elements shed from the surface of the primary tumor would mostly find their way into the pelvis, and probably here found conditions favourable to their attachment and development. Though the evidence offered is but small, it affords an analogy to what occurs in tubercle of the larynx. Here primary tubercle is rare, whereas secondary to tubercle of the lung it is rather frequent, owing, I believe, to the constant passage and lodging of phthisical expectoration about the upper parts of the larynx, where the bacilli appear to be able to fix themselves and to produce their characteristic results.

The possibility of producing malignant growths by experimental inoculations in man is obviously a question likely to remain undecided, but in animals suitable conditions might be found if the subject of an epitheliomatous tumor were taken, and a scraping from the most flourishing part of its tumor placed on a wounded surface which was commencing to cicatrise, on the same animal. Under such conditions healthy epithelium would grow sturdily, and so one would imagine so-called malignant epithelium might if ever its transplantation is to be effected, for not only are the local conditions favourable,

but the constitutional also if these be necessary to the success of the experiment.

The summing up of all this, however, but brings me back to the statement made a few minutes since, that we are not yet in a position to grapple with the problem of malignancy. Every effort towards a solution of that problem is needed, and help towards this may be given by clinicians as well as by pathologists, especially in those instances now known as cases of traumatic malignancy. Accurate observation and exact record of these, with careful histological and experimental investigation may, I think, in the future afford valuable help towards the elucidation of some of those points to which I have drawn your attention.

It now remains to me only to thank you, Gentlemen, for the considerate attention you have given to my remarks, and to apologise for the imperfect manner in which I have discussed the topics under consideration.

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