The Erasmus Wilson lectures on the general pathology of tumours : delivered before the Royal College of Surgeons of England on February 10th, 12th, and 14th, 1902 / by Charles Powell White.

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ON

THE GENERAL PATHOLOGY OF TUMOURS

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LECTURE I.

Delivered on Feb. 10th.

MR. PRESIDENT AND GENTLEMEN,—My first duty is to thank you for the honour that you have done me in appointing me to deliver this course of lectures and to express the hope that they will prove of interest to you.

In undertaking pathological research there are three methods that we can adopt: we can either consider the diseases of some particular region of the body, or we can consider separate branches of pathology, such as histology, bacteriology, pathological chemistry, or experimental pathology, or we can consider the different pathological processes which give rise to the phenomena of disease, collecting the necessary facts from different regions and by different means of research. The adoption of the first two methods without correlating the results by the third tends to produce a certain narrowness of mind which is not to the best interest of pathology. For instance, the bacteriologist tends to look upon the microbe as the be all and end all of disease, while the pathological chemist attempts to find the necessary factor in the many chemical products of metabolism. Those, also, who confine their attention to a particular region of the body tend to form ideas of pathology which are adapted to that region only. Now diseases are characterised by certain pathological processes, and these processes are essentially the same, whatever the organ or tissue involved. If we wish, then, to investigate any pathological process we must call to our aid all regions of the body and all methods of research. My own observations have been almost entirely histological. It is sometimes alleged that histology has said its last word in pathology, but this is by no means true. There still remains an immense field for research, more especially in the study of serial sections and in the minute cytological studies which have been up to the present time left mainly to the biologists.

The subject of these lectures—the general pathology of tumours—is one of surpassing interest both from the

scientific and from the practical point of view ; it is a subject which, in its broader aspects, has received little attention of late years, most recent work having been confined to the study of the malignant growths alone.

In the old days of humoral pathology tumours, like other conditions, were ascribed to the action of one of the so-called vicious humours ; later, the blood, and then the lymph, was supposed to play the all-important part ; then came the assumption of an hypothetical fluid ("blastema") from which tumours were supposed to separate out by a process akin to crystallisation. After Virchow had shown that every cell was derived from a pre-existing cell, the chief share in tumour causation was given to chronic irritation in spite of the fact that irritation might be prolonged for an indefinite time without giving rise to the development of a tumour. Cohnheim and others attempted to find the common factor in the embryonic rudiment from which all tumours were supposed to originate, but they were obliged to exclude certain cases of undoubted tumour formation. Lastly, of late years, we have seen pathologists endeavouring to find a parasitic origin for sarcoma and carcinoma, although it is impossible, on this supposition, to explain the occurrence of congenital sarcomata. It is evident, then, that the common factor in the pathology of tumour formation has not yet been found, and it is with the idea of attempting to discover this common factor that I have been studying the pathology of tumour formation for the last four or five years. Early in my research it became evident that I could not limit myself to tumours alone, for they form part of a larger group of pathological conditions all of which have to be considered together. In these lectures, therefore, I propose to indicate the direction in which this common factor is to be looked for, and to do this I shall consider in order the classification, life-history, and causation of tumours.

Classification.

Two methods have been adopted for the classification of tumours for pathological purposes ; one based on embryology, the other on the histological structure. Now a classification based on embryology is unsatisfactory because an arbitrary period of development is chosen as the starting point—namely, that period in which the embryo consists of three layers, and yet, in spite of this threefold basis, tumours are divided into two primary classes only. It is also unscientific because, since a large portion, at least, of the epithelium of the genito-urinary tract is derived from the mesoblast, it is possible for any kind of epithelial tumour to arise from any one of the three layers. We should, therefore, have epithelial tumours occurring in both of the primary classes and, in consequence, from an examination of any particular tumour, it would be impossible to decide in which class it should be

placed. Those who have adopted this method have never carried it out completely ; they have assumed that, contrary to the generally accepted views of embryologists, epithelium does not arise from the mesoblast, and they include in the mesoblastic group such tumours as the neuromata and gliomata, which are epiblastic in origin. We can, therefore, conclude that an embryological system of classification is of no use at all. A classification based on histology is not open to these objections ; the basis—namely, the histological structure—being a well-defined one, we can, by an examination of any particular tumour, readily determine to which class it belongs.

Having decided, then, that the classification is to be founded on a histological basis, we have next to consider the method by which the different classes can be best formed. The method of which I shall make use is substantially the same as that which I published about three years ago.[1] The ultimate morphological elements of which the organism is composed are the *cells*. It is unfortunate that we have no satisfactory terminology to express the various kinds of cells, but have to make use of such cumbersome expressions as "connective tissue cells," &c. I would suggest that, following the precedent set by the terms "leucocyte," "phagocyte," &c., we should make use of the termination *cyte* to express the meaning *cell*, so that we should have the terms "fibrocyte," "chondrocyte," &c. Epithelial cells might be called "epicytes" and a general term for the connective tissue cells would be found in the term "desmocyte." We should thus have a uniform system of cellular terminology. The cells immediately resulting from the cleavage of the ovum are *indifferent cells* —that is, the individual cells have no characteristics which distinguish them from each other, and in the course of development similar cells may give rise to very different structures. As development proceeds the cells become differentiated into two great classes : (1) cells which in the course of proliferation remain in contact with each other, covering surfaces and lining tubes—namely, epithelial (including endothelial) cells ; and (2) cells which in the course of multiplication become separated by intercellular substance or by connective tissue, such as the connective tissue cells, muscle cells, and nerve cells. These last might be collectively named "mesocytes." Now in order that the cells may fulfil their proper functions they are arranged in a definite and orderly manner. These arrangements of cells are called "*tissues*" and are of two kinds : (1) special tissues which have special functions to perform, and (2) connective tissues which act as supports to the special tissues. Again, in order that the tissues may properly perform their functions they are arranged among themselves so as to form *organs*. The organs are, in their turn, so arranged as to form the organism.

[1] Journal of Pathology and Bacteriology, vol. vi.

Starting from this threefold basis we arrive at a simple and satisfactory classification of tumours. Firstly, taking them in the reverse order, we have a class of organ tumours or organomata. In these tumours we can recognise distinct organs or parts of organs which, however, are not arranged so as to form a body or part of a body. The best known example of this class is the dermoid cyst, in which can be recognised skin, teeth, bones, &c., which are arranged indiscriminately. Secondly, we have a class of tissue tumours or histiomata in which we can recognise distinct tissues which, however, are not arranged among themselves so as to form organs. A fibroma, for example, is a mass of fibrous tissue which is not arranged so as to form a tendon or fascia. Each of the tissues of the body has its representative tumour in this class. Lastly, we have a class of tumours which can be called cell tumours or cytomata, in which we can recognise the cells which, however, are not arranged, at any rate in their growing portions, so as to form tissues. In this class we have carcinomata derived from epithelial and endothelial cells and sarcomata from connective tissue (and muscle) cells. We also have certain tumours which do not fall under the heading either of "sarcoma" or of "carcinoma"; they have been called by various names such as "adenosarcoma," "sarcoma carcinomatodes," &c., and they have sometimes been called "teratomata." thus confusing them with such tumours as dermoid cysts, &c. As I propose to form a new genus for these tumours, I must justify myself by giving a description of their histological characters. These tumours are most frequently met with in the genito-urinary tract, especially in the kidney where they are usually congenital, they are also found in the parotid region and in the liver and I have seen a case in the roof of the naso-pharynx. As met with in the kidney these tumours are seen to be composed mainly of round cells resembling those of a round-celled sarcoma; these cells may be called the primary cells of the tumour. Imbedded in this sarcoma-like tissue are a number of epithelial tubes which may be simple in form or irregular and branched. In some places these tubes may form cysts which may contain intra-cystic growths. In other places may be found spindle cells and striated muscle fibres; fat and mucous tissue may also be present. On more minute examination the epithelial tubes are seen not to be sharply marked off from the sarcoma-like tissue, but the cells of the tubes pass imperceptibly into the surrounding cells. If serial sections are made the tubes are found not to be connected together but to lie completely isolated among the primary cells. The other tissues present also shade off gradually into the surrounding cells. The tubes can be seen to arise by a circular grouping of the primary cells. At first this group has in its centre a mass of homogeneous material apparently derived from the cell bodies; later this material disappears, leaving a central lumen in the group of cells

which have now taken on epithelial characters. In some cases the tubes are occupied by a mass of flattened epithelial cells resembling squamous cells. Some of the tubes undergo further changes by the ingrowing of the wall on one side so as to make the lumen assume a crescentric shape on section. When this is the case the epithelium on the outer concave border of the crescent becomes flattened so as to resemble endothelium, the epithelium covering the ingrowth retaining its cubical form. The whole resembles exactly an embryonic Malpighian body with its capsule of Bowman and glomerular tuft before the capillaries have entered it. The explanation of these appearances is to be found as follows. The primary cells of the tumour are to be regarded as indifferent cells derived from the intermediate cell-mass of the embryo ; these cells, as they proliferate, undergo differentiation, some forming epithelium, others muscular fibres and other structures which may be present. In fact, just as sarcoma is a tumour of connective tissue cells and carcinoma of epithelial cells, so these tumours are tumours of indifferent cells ; and just as in sarcoma some of the cells may form definite connective tissue of different kinds, and as in carcinoma some may form epithelial tubes, so in these tumours some of the cells may undergo differentiation and form epithelium and the other kinds of tissue that are met with. Similar appearances are seen in some parotid tumours. In these growths the primary cells are often irregular in shape and have numerous protoplasmic bridges connecting the adjacent cells with each other, resembling the prickle cells of squamous epithelium. If different parts of the tumour are examined it is found that, on the one hand, the cells become separated and the protoplasmic bridges lengthened by the interposition of a homogeneous intercellular substance, thus forming typical mucous tissue or cartilage ; while, on the other hand, by a closer apposition of the cells they come in contact and form epithelial tubes which at first contain, as in the kidney tumour, a homogeneous substance which subsequently disappears. These tubes are, as in the former case, isolated among the primary cells of the tumour. Other observers have held the same views as regards these kidney tumours. Mr. F. T. Paul in 1886[2] was of the opinion that they grow out of a developmental abnormality while the tissues of the embryo are still in an imperfect state of differentiation ; and Mr. Keith W. Monsarrat[3] states that they are traceable to a perversion of the cellular elements from which, under normal development, the Malpighian bodies and convoluted tubules should arise. Mr. Monsarrat is of the opinion that the sarcoma-like cells arise by proliferation from the epithelial tubes, but he does not give any reason why the cells should be derived from the tubes rather than the tubes from the cells

[2] Transactions of the Pathological Society of London, 1886.

[3] Thompson Yates Laboratory Reports, vol. iii., Part 2.

as I have stated above. The fact that the tubes lie isolated in the midst of the sarcoma-like cells points to the view that they are of secondary formation. From these facts it is evident that these tumours are neither sarcomata nor carcinomata, and we are therefore justified in allotting them a distinct place in our classification. I propose for these tumours of indifferent cells the name of "blastomata," which name was, I think, first proposed by Dr. Herbert Snow in a somewhat similar sense.[4]

It would appear to be impossible to distinguish between undifferentiated cells and some forms of connective tissue cells. In fact, it is possible that the round cells of a round-celled sarcoma in reality correspond to these undifferentiated cells and that this growth is, therefore, a pure blastoma, but it is not worth while, on this account, to alter the name of this growth, since it would not serve any useful purpose and would only lead to confusion. The criterion, therefore, between a blastoma and a sarcoma is the fact that in the former some of the cells become differentiated into epithelial cells.

Although the characteristic of the cytomata is the fact that the cells are not arranged so as to form tissues, yet, in many cases, this is only true of their growing portions. In the older parts of the growth fully-formed tissues may be present. In columnar-celled carcinoma, for instance, we find well-formed epithelial tubes, and in sarcoma it is not uncommon to find fully-formed fibrous tissue, cartilage, or bone, and we have seen that in the blastomata differentiation and the formation of distinct tissues occur. The formed tissues are, however, of secondary development and not primary as in the histiomata.

In drawing up a tabular classification of tumours it must be remembered that the species and genera are not so well defined as in a classification in biology, hybrid tumours being frequently met with. If the different kinds of connective tissue tumours are regarded as species the different kinds of epithelial tumours must also be so regarded, so that if fibroma and chondroma are species, carcinoma, sarcoma, and myoma are genera. Under the term "teratoma" I should include only those tumours in which distinct organs, or parts of organs, without any regular arrangement, can be recognised. The term should not be used of a growth merely because it contains a variety of tissues, nor should it be applied to supernumerary limbs and other malformations. The tissue tumours are named by appending the suffix *oma* to a root which expresses the tissue which constitutes the essential part of the growth. Following this rule, the generic name for epithelial histiomata should be "epithelioma." This term has, however, unfortunately been applied to the corresponding cell tumours in which place it is redundant and wholly unnecessary. In consequence we have no

[4] Transactions of the Pathological Society of London, 1896.

generic or specific term for these growths, "adenoma" and "papilloma" being names given to varieties of the species of the genus epithelioma. I should include under the term "adenoma" any tumour which has as its characteristic feature tubes or spaces lined with epithelium whether or not it arises in connexion with a gland. Adenomata sometimes take origin from a surface epithelium as in the skin, in which case they are formed of tubes lined with squamous epithelium, and in the bladder when the tubes are lined with transitional epithelium. The fact that a tumour is composed of epithelial tubes does not necessarily imply that it arises from tubular structures. The term "neuroma" should be confined to those tumours which contain nerve-cells as well as nerve-fibres.

As regards compound terms in the nomenclature of tumours, I am of the opinion that they should be used according to some definite rule. The mere presence of different tissues in the same tumour is no ground for giving it a compound name, otherwise, since all tumours contain blood-vessels and connective tissue, every tumour would have a compound name. Compound names should be restricted to (1) tumours compounded of two or more species of the same genus, and (2) tumours compounded of the species of corresponding genera of the histiomata and cytomata. Thus we can speak of myxlipoma, osteochondroma, fibrosarcoma, &c., and we can also use the term "adenopapilloma." In other cases, if it is necessary to qualify the species it should be accomplished by using a qualifying adjective. We should thus speak of a fibrous adenoma or a vascular fibroma, &c.

With regard to the term "cancer" I would enter a plea for restoring to it the old meaning, as signifying any kind of malignant growth. As a synonym for carcinoma the term "cancer" is redundant and useless, whereas it would be of great use as synonymous with the more cumbrous term "malignant disease."

Classification of Tumours.

A. Organomata or Organ Tumours.

Teratoma (dermoid cyst).

B. Histiomata or Tissue Tumours.

(*a*) *Connective tissue tumours* (*desmomata*).—Fibrous tissue, fibroma ; fat, lipoma ; mucous tissue, myxoma ; notochordal tissue, chordoma (of Ribbert) ; cartilage, chondroma ; bone, osteoma ; and neuroglia, glioma.

(*b*) *Lymphoid tissue tumours* (*lymphomata*).—Lymph-adenoid tissue, lymphadenoma (lymphoma) ; and bone marrow, myeloma.

(*c*) *Muscle tumours* (*myomata*).—Smooth muscle, leiomyoma ; and striated muscle, rhabdomyoma.

(*d*) *Nerve-tissue tumours* (*neuromata*).—Medullated nerve-tissue, myelinic neuroma ; and non-medullated nerve-tissue, amyelinic neuroma.

(*e*) *Epithelial tissue tumours* (*epitheliomata*).—Squamous epithelium, squamous adenoma and squamous papilloma ; columnar epithelium, columnar adenoma and columnar papilloma ; spheroidal epithelium, spheroidal adenoma ; and endothelium, angeioma and endothelial papilloma.

C. Cytomata of Cell Tumours.

(*a*) *Tumours of indifferent cells* (*blastomata*).

(*b*) *Tumours of connective tissue cells, also of lymphoid tissue cells and muscle cells* (*sarcomata*).—(1) Pure sarcomata : round cells, round-celled sarcoma ; spindle cells, spindle-celled sarcoma ; and giant cells, giant-celled sarcoma. (2) Compound sarcomata : fibrous tissue cells, fibro-sarcoma ; cartilage cells, chondro-sarcoma, &c.

(*c*) *Tumours of epithelial cells* (*carcinomata*).—Squamous cells, squamous carcinoma ; columnar cells, columnar carcinoma ; spheroidal cells, spheroidal carcinoma ; and endothelial cells, endothelial carcinoma.

From this scheme of classification we arrive at the definition of a tumour : a tumour is a mass of cells, tissues, or organs, resembling those normally present in the body, but arranged atypically, which grows at the expense of the body without at the same time subserving any useful purpose therein. It will be seen that the distinguishing peculiarity of tumours is that they are atypical, not in the structure, but in the arrangement of their component parts.

Having thus classified tumours by analytical methods let us now apply the opposite method of synthesis—that is, let us consider what other pathological processes are allied to tumour formation. Firstly, there are certain cases of progressive hypertrophy of organs which resemble tumours in many respects. Examples are to be found in the prostate, the breast, the spleen, the thyroid gland (goitre), the bones (leontiasis ossea), and possibly also in the lymphatic glands (Hodgkin's disease). In the next place there are certain cases where the whole of one tissue, usually the connective tissue, of an organ undergoes progressive hypertrophy. This is met with in the progressive fibrosis of nerves, in the prostate, where either the epithelium or the stroma may undergo a progressive increase, and possibly also in some cases of cirrhosis of the liver. Again, there are cases of progressive hyperergia or progressive increase of functional activity, such as is found in the kidneys

(in diabetes insipidus), in the leucocyte-forming organs (in leucocythæmia), perhaps also in the thyroid gland (in Graves's disease). It is also found in many nervous and mental diseases and in diseases of metabolism. Lastly, there are cases of progressive metaplasia as, for example, in myositis ossificans. All these processes resemble tumour formation in the progressive character of their course and in the fact that they cannot be ascribed to definite extrinsic causal agents and, with tumour formation, they may collectively be called the "progressive processes."

Bearing in mind the foregoing scheme of classification, we can draw the following conclusions. 1. Every kind of tissue in the body has its representative tissue tumour. 2. Every kind of cell, with the exception of nerve-cells, has its representative cell tumour. Cell tumours of nerve-cells have not been described, but muscle cells are represented by myosarcoma, cartilage cells by chondro-sarcoma, and the different kinds of epithelial cells by the different kinds of carcinoma, &c. 3. Tumour formation is not an isolated process, but must be considered in its relation with other closely allied processes.

Rudiment of Origin.

I propose now to consider the life-history of tumours and shall commence by discussing the rudiments from which they arise.

Cohnheim [5] endeavoured to find the essential factor in tumour formation in the rudiments from which tumours take origin. According to him all tumours originate in rudiments composed of embryonic cells, separated in the early stages of development, which retain their embryonic characters for an indefinite period of time. It will be unnecessary for me to discuss this theory fully because no one, I imagine, at the present day believes that such a rudiment is a necessary antecedent to tumour formation. It will suffice to point out that this theory will not explain the occurrence of a tumour in a scar or chronic ulcer. Cohnheim himself recognised this difficulty and attempted to evade it by saying that these growths were not tumours in the proper sense of the word. Senn [6] endeavoured to surmount this difficulty by supposing that the rudiment of embryonic cells might be derived by proliferation from adult tissues. These rudiments of Cohnheim, with the exception of moles, have never been described and some of those which have been adduced in support of this theory do not fulfil the conditions laid down by Cohnheim.

Although tumours do not in all cases arise from embryonic rudiments there can be no doubt that they do so in some cases. It is well known that tumours may arise in moles

[5] Lectures on General Pathology.
[6] Pathology and Surgical Treatment of Tumours 1895.

which may be regarded as examples of these rudiments, and the theory would seem to be especially applicable to those tumours which I have called blastomata. In many cases, especially in papillomata and carcinomata, the tumour may be seen to rise directly in the normal tissues at the seat of origin. Some observers state that when this is the case they do not arise from the fully formed cells of the tissue but from the proliferative or mother cells. Undoubtedly tumours are more common in those tissues which exhibit the greatest proliferative capacity, or, in other words, in those tissues which display the greatest capacity for regeneration such as epithelium and connective tissue, but I see no difficulty in supposing that the adult cells, provided that they have not undergone any degenerative change, may undergo proliferation and thus give rise to a tumour. Cells which are in active division naturally assume a more elementary or, as it is called, embryonic condition, but to say, as some do, that before they can proliferate they must undergo a reversion to a more embryonic state is, in many cases at least, I think, to put the cart before the horse.

Tumours may also take origin in the tissues of a pre-existing tumour or in inflammatory products. Thus a carcinoma may arise in an adenoma, a sarcoma in a myoma or in the granulation tissue of a scar or ulcer.

Since the different forms of connective tissue are mutually convertible by the process known as metaplasia, it is not always necessary to presuppose a rudiment consisting of the same kind of tissue as that of which the tumour is composed. For example, since cartilage can arise in fibrous tissue, as is seen in drill bones, it is not necessary to suppose a cartilaginous rudiment to explain the origin of a chondroma. The size of the rudiment, or area of origin, of a tumour is variable ; in some cases it may involve the whole of an organ, while in others it may be very minute and it may conceivably consist of a single cell. With regard to the rudiment, then, we can draw the following conclusions. 1. The rudiment may consist (*a*) of a sequestrated collection of embryonic cells, such as described by Cohnheim ; (*b*) of the tissues normally present at the point of origin ; and (*c*) of tissues of new formation, either of inflammatory origin or the result of previous tumour growth. 2. It is not always necessary to presuppose a rudiment consisting of the same kind of tissue as that of which the tumour is composed. It is evident, therefore, that the common factor in tumour formation is not to be found in the rudiment from which the tumour originates.

Growth.

Having considered the rudiment from which the tumour springs we have next to direct our attention to the growth of the tumour from the rudiment. I shall postpone the

consideration of the processes of cell division for the present. Tumours grow mainly, if not entirely, by centrifugal growth—that is, by proliferation of their own cells. Coats and others have supposed that, in the case of carcinoma, increase takes place by centripetal growth, that is, by the epithelium in the neighbourhood of the advancing tumour taking a share in the growth, but the evidence in favour of this view is not convincing. Personally, I believe that the growth is centrifugal in all cases but that it is possible for the area of origin to extend by continuity. In some cases also it is possible that a malignant tumour may arise in multiple foci which subsequently fuse together. I agree with Ribbert that the examination of the growing margin of a tumour gives no information as to the structures from which it originated. Centrifugal growth may be either central or peripheral. If the growth is central the tumour will be definitely encapsuled ; if peripheral growth occurs the capsule will be more or less indistinct and the tumour will be infiltrating. In order to consider the origin and mode of growth in more detail, it will be necessary to treat of the different classes separately.

Organomata.—Many views have been held at different times as to the origin of the teratomata. Seeing that they occur most commonly in the ovary it is not unnatural to suppose that they originate in the germ-cells, either by the irregular development of a fertilised ovum or by a kind of parthenogenesis. This idea is unsatisfactory since, although the most complicated dermoids undoubtedly occur most frequently in the ovary, yet they are sometimes found in other parts of the body where germ-cells cannot be concerned. Nor is it sufficient to suppose that they arise in an abnormal inclusion of epiblast since the structures met with in these tumours are developed as much from the mesoblast as from the epiblast. These tumours must be considered as errors of development just as other tumours may be regarded as errors of growth, and the increase in size is accompanied by a process of development, a fact which distinguishes them from other tumours. For instance, the bones met with in dermoids are not merely irregular masses of osseous tissue such as are found in other growths, but are definite bones with a distinct periosteum although, the development taking place without reference to the needs of the organism, the bones thus formed do not, as a rule, bear any resemblance to any individual bones. The difference between teratomata and malformations consists in the fact that in the latter the organs are found to be arranged in a more or less typical manner such as occurs, for instance, in a limb, a condition which we do not find in a teratoma. As to the rudiment from which these tumours arise we do not know whether it consists of the structures usually present at the point of origin or of structures which have been included and are, in reality, derived from a distance.

Histiomata.—The growth of the tissue tumours takes place in exactly the same way as the growth of the normal tissues. The tissues of the tumour during growth always preserve their proper characters ; thus, the epithelium in an adenoma never loses its character as a tissue, it always forms a continuous membrane formed of cells in contact with each other lining tubes and spaces. Tissue tumours grow, for the most part, by central growth. Some fibromata, however, grow in part by peripheral growth and can therefore surround gland tubules, &c., so that they come to be imbedded in the tumour. The same is the case with some other tumours such as lipomata. The mode of growth in osteomata does not seem to have been determined ; many growths called osteomata are in reality ossifying chondromata. The true osteoma such as is met with in the skull sometimes involves both tables and, from its macroscopic appearances, would seem to increase by centrifugal growth, that is, by proliferation of the osteocytes themselves. This mode of growth would be in conformity with the growth of other tumours, but I have not had an opportunity of verifying it.

With regard to the epithelial histiomata the question arises : What part does the connective tissue play in the growth ? Many authors regard the stroma as playing an equal part with the epithelium. I, however, look upon it as altogether secondary in importance to the epithelium. As epithelium is an avascular tissue it is entirely dependent on the surrounding connective tissue for its nutrition. If, therefore, the epithelium proliferate, there must be a concomitant proliferation of the neighbouring connective tissue. Epithelial histiomata arise by a proliferation of epithelium which gives rise to an increase of surface area. This increase can only be provided for by the occurrence of one of two events : either the proliferating area projects above the surrounding surface or it becomes invaginated into the subjacent tissue ; in the former case the resulting tumour is a papilloma, in the latter it is an adenoma. In a papilloma the projecting area will necessarily carry with it a central core of fibrous tissue derived from the subjacent connective tissue of the part. Just as a papilloma may arise where there are normally no papillæ, so an adenoma may originate from a surface epithelium where there are no glands. I have seen a tumour of the bladder in which the epithelium, instead of projecting so as to form a papilloma as is usually the case, was invaginated into the subjacent tissue in the form of tubes lined with transitional epithelium without there being any penetration of the epithelial cells into the surrounding tissues, such as is the case in carcinoma ; the growth was, moreover, clinically benign in character. Structurally the tumour corresponded exactly with an ordinary adenomatous polypus of the rectum. Similar growths have been described in the skin by Bland-Sutton[7] and others. In this position,

[7] Transactions of the Pathological Society of London, 1892.

as in the bladder and rectum, they form pedunculated tumours formed of tubes lined with epithelium. In all probability such tumours have occasionally been described as carcinomata, but they can be distinguished by the fact that there is no tendency for the individual epithelial cells to penetrate into the surrounding tissues. Epithelial histiomata often present a combination of papilloma and adenoma, especially in the bladder and rectum.

With a view to studying the origin and growth of these epithelial tumours I have applied the method of serial sections. By this method the errors of interpretation which arise from the examination of a single section are entirely eliminated and we can obtain a mental picture of the complete structure of the tumour. Unfortunately it is difficult to obtain tumours of sufficiently small size for this method to be applicable. From the examination of an adenoma of the rectum by this method I came to the conclusion[8] that it arose, not from the crypts of Lieberkühn but from the surface epithelium, the tubes of which it was composed being new formed by invagination from the surface. A similar examination of the lobules of a large lobulated adenoma of the breast revealed the fact that all the epithelial tubes in the lobule were branches of a single tube which entered the lobule from the main tumour. It is probable, therefore, that all the tubes in an adenoma of the breast are in direct continuity with each other, and that therefore they arise from a single epithelial rudiment.

Cytomata.—The growth of the cell tumours differs from that of the tissue tumours in that the growing portions consist of cells more or less loosely held together but not forming definite tissues. These cells readily penetrate into the interstices of the surrounding tissues. Any formed tissues which may be present in cytomata are of secondary, not primary, formation.

Carcinomata arise from epithelium or endothelium. The area of origin may be localised or may involve the whole of an organ as in the rare cases of diffuse carcinosis met with in the breast and kidney. The stroma is derived from the surrounding tissues and represents the reaction of the tissues against the invading epithelial cells. The growth in carcinomata is almost entirely peripheral, and takes place by individual cells or small group of cells penetrating into the surrounding connective tissue spaces. This can be detected even in columnar-celled carcinomata, at the growing edge of which can be seen rows and groups of columnar cells invading the surrounding tissues, the tubes being secondary formations. The growth therefore differs entirely from that of an adenoma in which the growth takes place primarily in the form of tubes.

Sarcomata arise in any form of connective tissue and the

[8] Journal of Pathology and Bacteriology, vol. vii.

area of origin may be limited or may involve the whole of the connective tissue of an organ, as is seen in the rare cases of diffuse sarcoma of the liver. Growth is both central and peripheral, and there is often a secondary formation of definite tissues such as fibrous tissue or cartilage. I have already considered the growth of the blastomata.

Termination.

Tumours in most cases continue to increase in size without attaining to any final termination. In some cases a limit is reached owing to a change in structure such as ossification or calcification. In other cases, again, a tumour after growing for a time may become stationary. In rare cases a tumour may decrease in size and ultimately disappear, and this without undergoing ulceration or necrosis. Sir William H. Bennett, in a clinical lecture at St. George's Hospital about three years ago,[9] gave examples occurring in his practice which show the possibility of malignant growths completely disappearing without any special treatment. In four cases verified microscopically as sarcoma the patients regained perfect health, the tumours disappearing completely. One of these was an abdominal spindle-celled sarcoma, two were melanotic sarcomata with disseminated growths, and the other was a sarcoma of the testis. In two cases of carcinoma in which the primary growth was removed and in which recurrence took place the recurrent growths subsequently became smaller and eventually almost completely disappeared. In one of these cases the primary growth was in the testis and in the other it was in the breast, and both were verified microscopically. Another case of carcinoma of the breast (not verified) was known to have remained stationary for 15 years. Another was a case of malignant disease of the pylorus with obstruction ; this was not verified, but at the operation for gastro-jejunostomy numerous secondary growths in the omentum and under the liver were seen and handled. In this case the patient recovered completely and was well five years after the operation, no growths being then discoverable. He also mentions a case of apparently malignant disease of the cervical glands too extensive for operation in which the patient recovered. Besides these remarkable cases—and they were only examples of many more which had come under the observation of Sir William Bennett—there have been recorded lately many cases of carcinoma of the breast which have improved after the operation of oöphorectomy in combination with thyroid feeding and other cases which have improved without special treatment. It is, therefore, a mistake to say that a tumour always continues to grow without limit ; it may, under certain

[9] The Lancet, Jan. 7th, 1899, p. 3.

conditions which are imperfectly understood, become stationary or even diminish in size or disappear completely.

Physiological Characters.

We have next to consider whether the cells and tissues of which a tumour is composed are capable of behaving physiologically like the cells and tissues of normal organs, or, in other words, are the cells and tissues of a tumour capable of performing any function? In considering this question we have to remember the fact that the cells of a tumour are in a state of more or less rapid proliferation and we should not, therefore, expect to find them very active in the performance of any function. Moreover, owing to the atypical arrangement which is characteristic of a tumour, there is no mechanism by which the performance of a function can be initiated, and, for the same reason, any function that may be performed is incapable of being utilised. The muscle-cells of a myoma, for instance, are probably capable of contraction, but, owing to the want of nervous connexion and the atypical arrangement, this power of contraction is not manifested and, if it did take place, it would serve no useful purpose. In spite of this there are several facts which show that the cells of a tumour are capable of functionating. The sebaceous glands of a dermoid secrete sebum, the cells of an adenoma or carcinoma of the intestine secrete mucin, adenomata of the thyroid contain colloid, and adenomata of the breast sometimes contain a milky fluid. Also the cells of a squamous-celled carcinoma undergo keratinisation, those of a carcinoma of the stomach form pepsin and rennin, and those of a carcinoma of the pancreas contain all the ferments proper to the pancreas, and this is true, at any rate in the case of the pancreas, of secondary, as well as of primary, growths (Waring).[10]

Perhaps the most remarkable physiological characteristic of tumour-cells is the property which they possess of storing enormous quantities of glycogen. In this respect, according to Brault,[11] they far exceed all the normal cells of the body and they can only be compared with the rapidly proliferating cells of the embryo. Those tumours which grow the most rapidly contain the greatest amount of glycogen, and from the study of the amount contained in a tumour the rate of growth can be judged. The cells of carcinomata and sarcomata are loaded with glycogen, while the surrounding tissues show a complete absence of it. The presence of this glycogen raises some interesting points for our consideration. Firstly, what is the meaning of this great store of carbohydrate material? Carbohydrate material is the great source of energy in the living organism; it is to the body what the fuel is to the steam

[10] Journal of Anatomy and Physiology, vol. xxviii.
[11] Manuel d'Histologie Pathologique, Cornil and Ranvier, 1901.

engine. In the case of the embryo and in tumour formation energy is manifested by the multiplication of cells, and in order to supply this energy the cells store up carbohydrate in the form of glycogen. Secondly, what is the origin of the glycogen? Presumably it is formed in the same way as under normal conditions from the circulating glucose; if, however, the supply be deficient, it can be derived from the proteids of the body as in the severer forms of diabetes. Lastly, what becomes of the glycogen? Although there is such an enormous store of glycogen, yet, as far as I know, malignant disease is seldom or never accompanied by glycosuria. The glycogen is used up in the multiplication of cells because the central parts of a carcinoma, where proliferation has ceased, are completely free from it. It is probably directly oxidised and eliminated as carbon dioxide and water. This question of the presence of glycogen in tumours is well worth further study, especially by those who take a special interest in metabolic processes.

Pathological Changes.

The pathological changes to which tumours are subject need not detain us since they are the same to which any normal tissue is liable. Tumours are liable to the various retrogressive processes, especially to mucoid and fatty changes and calcification, to necrosis, to inflammation and repair, and to the formation of new tumours.

Clinical Characters.

It will be noticed that in the classification which I have given the histiomata and cytomata correspond respectively to the simple and malignant tumours of a clinical classification. Most authors state that tumours, usually simple, may occasionally take on malignant characters, and this is especially supposed to be the case with chondromata. This idea is based chiefly on a case reported by Paget of a chondroma of the testis which gave rise to metastatic growths in the lungs and elsewhere. This case, however, was re-investigated by Kanthack and Pigg,[12] who found that it was not a pure chondroma, but that it contained carcinomatous elements, and in the same way it will, I think, be found that whenever a tumour that is apparently a tissue tumour displays malignant properties it is in reality a cell tumour.

In my opinion the difference between simple and malignant tumours is to be found in the manner in which they grow. The growing area of a cell tumour consists of cells, either separate or in small groups, not forming any definite tissue, any formed tissues that may be present in the tumour being of secondary formation. The tissues in a tissue tumour, on

[12] Journal of Pathology and Bacteriology, vol. v.

the other hand, are of primary formation. For example, the growing area of a columnar-celled carcinoma consists of columnar cells in rows or groups which only secondarily give rise to epithelial tubes, whereas in an adenoma the growing area consists of epithelial tubes similar to those in the older parts of the tumour. Similarly in a chondro-sarcoma the growing area consists of collections of cells which only secondarily form cartilage, while in a chondroma the cartilage grows in the same way as under normal conditions.

The mode of growth in cell tumours readily explains how it is that these tumours penetrate the surrounding structures instead of merely displacing them and how the cells find their way into the lymphatics and blood-vessels and so come to be distributed to distant organs.

The wasting and cachexia by which malignant tumours are often accompanied may probably be explained by the drain of nutritive material, especially carbohydrate, caused by the rapidly growing tumour.

The clinical features of malignant disease are very imperfectly dealt with in most books. The ordinary text-books of medicine—even Allbutt's System of Medicine—are silent on the medical aspects of carcinoma and sarcoma and little is to be gathered from other sources. There seems to be no full account of the temperature and urine, and the blood has not received the attention that it deserves. We require much more information as to these points, especially with regard to the excretion of nitrogen.

LECTURE II.

Delivered on Feb. 12th.

MR. PRESIDENT AND GENTLEMEN,—In this lecture I propose to consider certain theories which have been advanced to explain the causation of tumours, but it will first be necessary to draw your attention to the minute structure of the cell and to the changes which it undergoes during the process of cell division.

CELL STRUCTURE AND CELL DIVISION.

In the normal cell at rest the following constituents can be recognised.[13] 1. The *cytoplasm* or protoplasm of the cell body. 2. The *nucleus*, which consists of the following parts: (*a*) the *nuclear membrane*, which gives to the nucleus its sharp contour; (*b*) the *nuclear reticulum*, which consists partly of chromatin, which is the most important constituent and which gives to the nucleus its intense staining properties, and partly of linin, which resembles the cytoplasm in staining reactions; (*c*) the *nucleoli*, of which there are two kinds, the *plasmosomes* or true nucleoli, which stain like the cytoplasm, and the *karyosomes*, which stain like the chromatic substance; and (*d*) the *karyolymph*, which occupies the meshes of the nuclear reticulum. 3. Lastly, there is the *centrosome*, which is usually situated in the cytoplasm, but which is occasionally found in the nucleus. The centrosome is a permanent constituent of some cells, but it has not been shown to be so in all. It appears as a minute body staining with the nuclear dyes and is surrounded by a spherical body known as the *centrosphere* or attraction sphere. From the centrosome there often radiate achromatic fibres forming the *aster*. The functions of the centrosome are not yet fully known, but there are reasons for regarding it as the dynamic centre of the cell—that is, the centre which regulates the movements of the cell. In some cells the centrosome has been found to have intimate relations with the cilia; this is especially the case in the spermatozoon in which the centrosome is found in the middle piece at the attachment of the tail. In the leucocyte the centrosome and aster are permanent and are supposed by

[13] Wilson: The Cell in Development and Inheritance.

some to influence the amœboid movements. In epithelia cells the centrosome is usually found towards the free border of the cell. The chromatin of the nucleus at rest is arranged in the form of a network. Now, the first indication of division of the cell by mitosis is found in the centrosom- which divides. This division sometimes takes place immee diately after the preceding division, so that the centrosome in the resting cell often appears double. The two halves then separate and, at the same time, there appears a structure composed of achromatic fibres known as the *amphiaster*, which consists of an aster at each end with its centre at the centrosome and the intervening *achromatic spindle* uniting the two centrosomes. At the same time that these changes are taking place in the centrosome the nucleus undergoes alterations; the chromatin becomes arranged in the form of a skein or *spireme*, which then splits into a certain number of segments called *chromosomes*, which are themselves composed of minute granules called *chromomeres*. The chromomeres next undergo division in such a way that each chromosome comes to consist of two parallel rows of chromomeres. The nuclear membrane has by this time disappeared and the chromosomes are drawn into the axis of the achromatic spindle, to the fibres of which they become attached. The two halves of the chromosomes, then, under the influence of the achromatic fibres, become separated and pass towards the centrosomes and finally rearrange themselves so as to form the nuclei of the daughter cells. The cell body begins to divide as the chromosomes separate, apparently also under the influence of the achromatic substance. We thus see that, while the division of the chromosomes is spontaneous, their separation is due to the action of the centrosomes and the amphiaster and that, in consequence, the centrosome should be considered as the prime agent in the division of the cell.

The centrosome and its associated achromatic substance or *archoplasm* have been strangely neglected by pathologists, although they form such an important part of the cell. Under normal conditions the result of mitosis is that each daughter cell contains exactly the same number of chromosomes as the mother cell, this number being fixed for each species of animal. In animals multiplying by sexual reproduction this number is always even, and in man it is said to be 16. I have been able to verify this number in the case of a few carcinoma cells which I have come across in which it has been possible to enumerate the distinct chromosomes.

In malignant growths and in some other conditions accompanied by rapid proliferation we often find a deviation from the typical form of mitosis; thus we find *asymmetrical mitosis*, in which the daughter cells contain an unequal number of chromosomes, and *multipolar mitosis*, in which the cell divides simultaneously into more than two daughter cells. Multipolar mitosis arises from the division of the centrosome into more than two parts; each part is

associated with a cone of achromatic fibres which passes to the chromosomes. I have not been able to determine the number of chromosomes in the daughter nuclei in these cases. In most cases of quadripolar mitosis which I have seen the daughter nuclei were not in the same plane but were at points corresponding to the angles of a regular tetrahedron.

Amitosis, or direct division, is often met with in malignant tumours and especially in those which are undergoing degeneration. In this mode of division the nucleus becomes divided in two by a septum ; the two halves then separate and this is followed by division of the cytoplasm. Frequently, however, the cell body fails to divide and thus arise cells with two or more nuclei. Another method of amitosis is described by Brault,[14] and from my own observations I can confirm his description. In this method the nucleus becomes drawn out into two or more parts, each part becoming the nucleus of a daughter cell. In other cases the nucleus may give off buds which form daughter nuclei. Occasionally the nucleus becomes split up into a number of chromatin particles of varying size which become scattered in the cytoplasm. That is known as fragmentation or *karyorrhexis.*

Endogenous formation of cells used to be thought a common event in carcinoma ; lately, however, doubts have been thrown on its existence, chiefly by those who uphold the parasitic theory. Personally I have no doubt that this process does occur and I should describe the method as follows. A portion of the nucleus becomes separated by fragmentation or budding, it then gathers round it some of the neighbouring cytoplasm which becomes separated from the rest of the cell body, and thus forms a daughter cell which gradually increases in size until it becomes a fully formed cell lying in a vacuole in the mother cell. In other cases the daughter cell is the result of an amitotic division in which one of the resulting cells lies within the other instead of separating from it as is usually the case. In this connexion it must be remembered that the chromomeres, of which the nuclear chromatin is composed, are, to a certain extent, living units capable of division and growth, so that it may be possible for a minute portion of the nucleus to grow so as to form the nucleus of a new cell. These included cells are of common occurrence in some carcinomata and sarcomata, and it is not uncommon to see a granddaughter cell within the daughter cell. I have proved by means of serial sections that these cells are really inclosed and not merely invaginated, and it is difficult to conceive how they come to be so inclosed unless they are formed *in situ.*

[14] Manuel d'Histologie Pathologique, Cornil and Ranvier.

Extrinsic Causes.

Causal factors may be divided into those which are of extrinsic and those which are of intrinsic origin. When we speak of a disease as a whole the term *extrinsic* implies that the factor is derived from outside the body ; when, however, a disease is considered in its relation to any particular organ the term implies that the causal factor is derived from outside that organ, but not necessarily from outside the body. Extrinsic factors undoubtedly play an important part in the causation of tumour formation. Tumours may arise as a result of chronic irritation such as that produced by constant friction or by the presence of a chronic ulcer ; they have also been ascribed to a blow or sudden injury as in the case of a sarcoma arising at the site of a fracture in a bone. These extrinsic factors, which are known by the general term *irritants*, are also the exciters of inflammatory processes, but there is this difference between the two cases. When inflammation follows the action of an irritant the amount of inflammation depends on the amount of irritation and on removing the irritant the inflammatory process ceases and the injury is made good ; in the case of a tumour following the action of an irritant, on the other hand, the action of the irritant may be momentary while the growth of the tumour is prolonged and the removal of the irritant does not cause the cessation of the tumour growth.

These extrinsic factors, therefore, cannot be the essential causal factors of tumour formation and can only be remote factors which act through the medium of intermediate intrinsic factors. We must, however, consider the possibility of the existence of a special extrinsic factor, such as an animal or vegetable parasite. The theory of parasitic causation of tumour formation has gained a large amount of acceptance at the present time and, indeed, almost all those who are working at the subject are approaching it from this point of view. This theory is only supposed to apply to those tumours which are malignant, but it is equally necessary to explain the formation of simple tumours if an extrinsic factor is thought to be essential at all, because the continuous and increasing growth of the tumour demands a continuous and increasing causal factor. I myself have not engaged in the search for a parasite although I have seen the bodies claimed to be of that nature. I have, however, studied minutely the histology and general pathology of tumours with a view to determining whether or not tumour formation can be explained by this theory and I have come to the conclusion that the essential causal factor cannot be found in any extrinsic irritant, whether parasitic or not. On account of the importance of this theory it is necessary to examine it closely and carefully to consider the arguments on both sides. In the following remarks I shall, for the sake of simplicity, use the term carcinoma, but the arguments will, as a rule, equally apply to sarcoma.

Parasitic Theory.

In discussing this theory, I shall first consider the basis on which it is founded, afterwards I shall consider in detail various objections which can be brought against it. The theory is based :—

1. *On the apparent resemblance of carcinoma to infective diseases such as tuberculosis.*—Carcinoma, at first sight, closely resembles tuberculosis in many respects. Both have a local origin and give rise to secondary deposits, first in the regional lymphatic glands, and later in the various organs of the body. When, however, we come to study the histology of the lesions in the two cases, the resemblance at once disappears. We find that the tuberculous nodule is made up of cells which are derived partly from cells which have exuded from the blood-vessels, and partly from the tissues of the part in which the bacillus has settled. A carcinomatous nodule, on the other hand, is composed of cells which are derived in secondary growths not from the part in which the growth is situated, but from the primary tumour, wherever this may be placed. We can, indeed, compare the epithelial cells of the carcinomatous nodule with the bacilli in a tubercle, and if we do this the analogy between the two diseases is complete, the stroma of the carcinoma corresponding to the histological tubercle, while the epithelial cells correspond with the bacilli in the tubercle. If, however, the comparison is made in this way the argument in favour of the parasitic origin of carcinoma from the analogy with tuberculosis completely fails, because, if we grant that the tubercle bacilli are capable of spontaneous proliferation, we cannot argue that their analogues, the epithelial cells of a carcinoma, can only proliferate under the influence of a parasite.

2. *On the inoculability of malignant growths.*—A few cases are on record in which a patient afflicted with carcinoma has apparently infected another person with the disease ; these cases are, however, extremely rare and would seem to be no more than coincidences. If tumours were due to parasites we should expect the infectivity to be much more marked. Growths are sometimes met with on the genital organs of bulldogs ; they have been especially described by Washbourn and Bellingham Smith [15] under the name of infective sarcomata. These growths are highly contagious but show only a slight degree of malignancy ; they are slow of growth and rarely give rise to metastasis and they cannot be transferred to any animals except dogs. Microscopically they closely resemble round-celled sarcomata. In two cases which I have had the opportunity of examining the growths had been present for 12 months and yet there was very little infiltration of the surrounding parts. Both were situated in the

[15] Brit. Med. Jour., vol. ii., 1898.

vagina and in one case there was a secondary growth in one of the mammary glands, yet, notwithstanding this, a complete cure took place after the removal of the affected part of the vagina and the secondary growth. As, therefore, these growths differ so largely from sarcomata as we meet them in man, we must be careful how we use them as an argument in favour of the parasitic theory. The fact that a tumour is inoculable does not necessarily imply that it is due to a parasite. The infective agent may very well be the epithelial cells themselves, since it must not be forgotten that they are living units. In skin-grafting we see that epithelial cells can be transplanted and, if this is true of normal cells, it is probably true also of the cells of a carcinoma. Malignant tumours have been successfully transferred from one animal to another but only if the two animals are of the same species.

3. *On the analogy with the lesions produced in the rabbit's liver and elsewhere by the coccidium oviforme.*—In coccidiosis of the liver we find numerous small cavities which are filled with the coccidia in various stages of development. On examining these spaces we find that they are lined by columnar epithelium and are evidently local dilatations of the bile-ducts. The younger forms of the parasite are found within the epithelial cells while the older are lying free in the cavity. This has been regarded as an example of true tumour formation caused by a parasite. I have not myself examined critically many of these cases, but from what I have seen I am more inclined to look upon them as a kind of retention cyst caused by the accumulation of the parasites in much the same way as bronchiectasis may be due to the accumulation of the bronchial secretion. The proliferation of the epithelium would in that case be of the same nature as that found in catarrhal inflammation. Occasionally the parasites are found in a cavity in the connective tissue and in that case the wall of the cavity consists of fibrous tissue without any epithelial lining, as would be the case with any other chronic irritant. In any case we do not in coccidiosis find the essential lesion of carcinoma—namely, penetration of the connective tissue by the epithelial cells,—so that if any conclusion is to be drawn from the supposed analogy it is that non-malignant tumours are caused by parasites.

4. *On the topographical distribution of carcinoma.*—Carcinoma may in a sense be called a disease of civilisation—that is, it is more frequent among civilised nations than among savages and it is more common among domesticated than among wild animals. It is said to be more frequent in valleys the rivers of which are liable to floods. These are conditions which affect the general health and it does not seem necessary to assume a parasite in explanation. In some places there are said to be certain houses the inmates of which are more liable to cancer than are those of other

houses, but we require more information on this point before we can draw any conclusions from it.

The above four facts are the bases on which is founded the general idea that malignant growths are due to parasites. There remains to be considered the question whether carcinoma is due to certain bodies described as parasites which are found in the tumour cells. From time to time during the last 11 years certain structures which are found within and between the cells of carcinomata have been described by numerous observers as parasites. There is, however, no agreement among the different observers as to the nature of these bodies nor as to which of the various cell inclusions are and which are not parasitic in nature. Two of the best papers which have been published of late years on this subject are those by Plimmer[16] and Gaylord.[17] Plimmer describes the parasite as a round body varying in size from 0·004 to 0·04 millimetre or more in diameter. In the centre is a minute body which he calls a nucleus, although, as he says, it probably does not correspond with the nucleus of an ordinary cell. Round the nucleus is a layer of homogeneous protoplasm which is bounded by a definite capsule. According to Plimmer, the nucleus of the parasite differs from the nucleus of a cell in its staining properties by refusing basic stains such as hæmatoxylin and staining with acid stains such as acid fuchsin. The parasites are found only in the growing edge of the tumour and are absent from the centre ; they are said to multiply by fission and segmentation, and perhaps, also, by budding. He found them in 1130 out of 1278 cases of carcinoma. Gaylord accepts Plimmer's bodies as parasites and also includes other forms such as Russell's fuchsin bodies. He relies chiefly on unstained specimens, but in an investigation of numerous specimens by Plimmer's methods he found them in every case of carcinoma and sarcoma that he examined and also in specimens of myxoma, adeno-fibroma, colloid goitre, and syphilitic lymphatic glands. According to him the parasites in the fresh state closely resemble fat globules from which, however, they can be distinguished by the fact that they are insoluble in ether and that they do not react like fat to osmic acid. He further states that the parasites can be detected in the blood of all cases of carcinoma and sarcoma in which cachexia is well marked. In opposition to Plimmer he says that the fluid obtained from the centre of carcinomata which have undergone degeneration consists practically of a pure culture or the organism.

As regards the cultivation of these parasites Plimmer was able from one case of carcinoma of the breast to isolate an organism which he identified as a blastomyces, and he was able by inoculating guinea-pigs to produce growths of endo-

[16] Practitioner, April, 1899.
[17] American Journal of Medical Sciences, May, 1901.

thelial origin in which he could recognise the organisms. Gaylord, on the other hand, working with a pure culture of Plimmer's yeast, was unable to reproduce in inoculated guinea-pigs bodies having a similar appearance to those met with in carcinoma. The results of inoculation were of a granulomatous nature. He was unable to obtain a culture of blastomyces from carcinomata except in one case, although he used as many as 64 different kinds of culture medium. Gaylord, by inoculating guinea-pigs with ascitic fluid derived from a case of carcinoma of the peritoneum, claims to have been able to produce nodules in the lungs which had some resemblance to carcinoma, but, judging from his illustrations, these nodules bear a close resemblance to the lymphoid nodules which are normally present in a guinea-pig's lung. His researches are being continued and we are promised a further communication on the subject.

We thus see that these two observers, both ardent advocates of the parasitic theory, differ from each other on some important points. Now it will be said, If these bodies are not parasites what are they? The answer to this question involves a consideration of the different inclusions which may be met with in carcinoma. Firstly, the cells of carcinomata are prone to degenerations of different kinds such as fatty, hyaline, colloid, and mucoid changes. According to the two observers, the parasites can readily be distinguished from the appearances due to these changes. The case, however, on which Gaylord made most of his observations was one of colloid carcinoma. Many pathologists, also, regard Russell's fuchsin bodies as resulting from hyaline degeneration. In the next place we meet with leucocytes and, occasionally, red corpuscles included in carcinoma cells. Of these, the red corpuscles would give rise to the greatest difficulty, but with reasonable care they should be readily distinguished. Then there are various appearances dependent on the rapid and irregular division of the cells, and it is here that the greatest difficulty would present itself. I have frequently seen a particle of chromatin which has become detached from the nucleus surrounded by a layer of protoplasm lying in the protoplasm of the epithelial cell, the whole forming a body exactly resembling one of Plimmer's bodies except that the nucleus stained with basic dyes. It is difficult to suppose that bodies so exactly similar should be of such entirely different characters, and I think it justifiable to suppose that those bodies in which the nucleus takes the acid stain may be of the same nature as those in which the nucleus stains with the basic dye, the nucleus having, perhaps, undergone some change which alters its staining properties. Gaylord states that he has succeeded in staining the nuclei of Plimmer's bodies with hæmatoxylin.

The various stages of endogenous formation may account for some of the structures supposed to be parasites. Sections through a daughter cell inclosed within a mother cell which

do not pass through the nucleus of the daughter cell give rise to the appearance of a non-nucleated body lying in the epithelial cell such as is shown in one of Gaylord's illustrations. Again, nucleoli, especially plasmosomes, frequently escape from the nucleus into the protoplasm and give rise to bodies closely resembling the so-called parasites. Lastly, there are the centrosphere and its contained centrosome. Borrel,[18] who is in favour of the parasitic theory, has shown that alterations in the attraction sphere may give rise to exactly the same appearances as those described as parasites, and I think that no one who has seen the illustrations of his paper can have any doubt that the appearances which he ascribes to variations of the attraction sphere are the same as those which others ascribe to the parasites. In the spermatocytes of the testis of the guinea-pig there are bodies of archoplasmic origin which are sometimes called "paranuclei." These bodies are round and may contain one or more centrosomes ; they stain with acid dyes and sometimes show a central spot which takes the stain more deeply than the periphery. They vary in size, some of them being almost as large as the nucleus. Like Plimmer's bodies, they are not found in cells which are undergoing mitosis. I am certain that if these bodies were seen in the cells of a carcinoma they would be at once branded as parasites. The appearances described by Plimmer as being characteristic of the parasites could all be explained on the assumption that they are of archoplasmic origin. Therefore, before these bodies are accepted as parasites the possibility of their being derived from pre-existing cell-structures must be fully considered.

From the foregoing remarks it will be seen that the grounds on which the parasitic theory is based are by no means satisfactory. I must next consider various objections to the theory. In the first place, as I have pointed out elsewhere,[19] we know of no disease characterised by definite anatomical lesions which is at the same time characterised by a definite extrinsic causal factor ; neither do we know of any disease characterised by a definite extrinsic factor which is at the same time characterised by definite lesions. Therefore, since tumours are characterised by their anatomical structure, we should not expect them to be due to definite extrinsic causal agents. In the next place, we know of no parasites which are capable of producing primarily a proliferation of cells. Adami[20] is somewhat inconsistent on this point, for he says in one place that proliferation is an intrinsic property of the cell and is only influenced indirectly by external conditions and in another place he states that an irritant which, when concentrated, produces destruction, when diluted produces proliferation. In the case of all known parasites the first effect is injury

[18] Annales de l'Institut Pasteur, February, 1901.

[19] Relation between Cause and Effect in Disease, Brit. Med. Jour., vol. ii., 1900.

[20] Brit. Med. Jour., vol. i., 1901.

or destruction, any proliferation which subsequently takes place being compensatory in nature to replace the cells which have been destroyed. I am not convinced that the proliferation of epithelial cells in coccidiosis is primary—that is, that the parasite directly causes proliferation. Even if a parasite were capable of causing a primary proliferation it would not explain the occurrence of a carcinoma since the essential lesion of carcinoma is not proliferation but is penetration of the epithelial cells into the connective tissue. In the next place, the reaction of the organism against all known parasites, animal and vegetable, is of a defensive nature and characterised by the phenomena of inflammation. The parasite first gives rise to injury or destruction of the tissues : this is followed by exudation of leucocytes which remove the damaged tissue and, if possible, the parasite, and this again by proliferation of the surrounding tissue which repairs the injury. A tuberculous nodule, for instance. is formed by centripetal proliferation of the surrounding tissue—that is, by proliferation taking place towards the irritant. It is far otherwise in carcinoma ; here we have proliferation taking place in a centrifugal direction away from the supposed parasite and, instead of a defensive reaction, there is produced an ever-increasing amount of epithelial tissue in which the parasite can grow and multiply. In fact, the organism would seem to welcome the parasite instead of repelling it. This is so opposed to the accepted laws of parasitism that one may be excused for doubting its possibility. Some have supposed that the parasite acts on the cell in somewhat the same way as a sperm cell acts on a germ cell and thus induces proliferation. This seems to me a very far-fetched and unwarrantable supposition and is negatived by the fact that, as regards the parasites that have been described, the parasite-containing cell does not undergo division. To make sure of this fact, which was mentioned by Ruffer and Plimmer,[21] I recently wrote to Mr. Plimmer and he tells me that the cells which contain the inclusion do not divide, but, as a rule, begin to show degenerative changes similar to those in phagocytic cells in other diseases when the cells cannot conquer. These degenerative changes would, however, seem to be very slight in amount.

As regards the relation between the supposed parasite and the cell, we have to consider how the parasite, in the case of intracellular parasites, enters the cell. Is the entrance active on the part of the parasite or passive as in phagocytosis ? or does the parasite fulfil its whole cycle within the cell ? The last supposition is impossible, for, since the containing cell does not divide, the parasite would not have any opportunity of continuing its existence when the cell had degenerated. If the entrance is an active process on the part of the parasite it is difficult to understand how a

[21] Journal of Pathology and Bacteriology, vol. i.

parasite which causes destruction of the cell into which it enters can cause active proliferation of the surrounding cells. If, on the other hand, it is a phagocytic action on the part of the cell, how is it that the youngest forms of parasite which are described are either within or close to the nucleus? The abnormal increase in the phagocytic properties of the epithelial cells is left wholly unexplained. Mr. Plimmer tells me that there is not sufficient evidence to show whether the entrance of the parasite into the cell is active or passive.

An example of true defensive reaction is seen in catarrhal inflammation. In this the affected epithelial cells degenerate and are cast off, those that are left proliferating to take their place. In carcinoma, however, the affected cells are not cast off, but penetrate into the deeper tissues; it is, therefore, the exact opposite of a defensive reaction. If, therefore, carcinoma be due to a parasite, we have the curious phenomenon of the organism not attempting in any way to defend itself against an injurious parasite. This would be a unique occurrence in the processes of disease. It might be suggested that the parasites spread into the connective tissue and are followed by the proliferating epithelial cells. This is highly improbable and implies a mechanism of defence which is entirely unknown and yet there would seem to be no reason why the ordinary means of defence should not be available. Another objection to the theory is the fact that we are not told whether each species of carcinoma and sarcoma has its own parasite, or whether they are all due to the same parasite. The different species of carcinoma are usually so distinct that it is difficult to suppose that they are due to the same parasite. If this were the case we should expect to find the metastatic growths differing according to the kind of epithelium in which they occur. For instance, in the case of a squamous-celled carcinoma with secondary deposits in the liver we should expect to find the latter composed of spheroidal cells derived, by the action of the parasite, from the liver cells, but this is a state of things that we do not meet with. Moreover, if sarcoma and carcinoma are, as Plimmer and Gaylord suggest, due to the same parasite, how is it that we do not meet with a primary carcinoma giving rise to secondary sarcomatous deposits? If, on the other hand, each species has its own parasite, how are we to account for those tumours which show intermediate forms between the better marked species? In columnar-celled carcinoma of the uterus we occasionally find areas of squamous cells lying among and evidently formed from the columnar cells. There are also the highly complicated compound sarcomata which it would be impossible to explain on the supposition that each kind of sarcoma has its own parasite. Again, if each kind of tumour has its own parasite, we must suppose a series of parasites each of which are only capable of acting upon one kind of cell. It would therefore be

necessary to suppose different carcinoma parasites for each gland in the body and we should also have to suppose a different series of parasites for each species of animal. Either of these suppositions, therefore, lands us in inextricable difficulties.

The parasitic theory, then, will not explain the production and growth of the primary tumour, nor will it explain the different species and the manner in which they breed true. Will it explain metastasis? Here, at all events, this theory ought to be capable of affording an explanation, since it is this feature which has afforded the chief ground on which the theory is based. In reality, however, instead of assisting the explanation of this feature, it increases the difficulty.

A metastatic growth cannot be due simply to the presence of a parasite for if it were, we could not have a metastatic carcinoma in a position devoid of epithelium. We must therefore conclude that, besides the parasite, at least one epithelial cell must be transferred from the primary growth to form the mother cell of the secondary deposit, but this cell cannot be the cell in which the parasite is lodged, since the parasite-containing cells, at least in the case of the described parasites, do not proliferate but undergo degeneration. Therefore we must imagine a parasite and a cell independently conveyed to the site of the metastatic growth. Again, the adoption of this theory will not explain the situation of the primary growth. It will not explain, for instance, the frequency of malignant disease in the female organs of generation or the rarity of it in situations in which we should expect it to be frequent, such as the lungs and small intestine. Nor does it explain why the acini of the breast are more frequently affected than the ducts. In the case of sarcoma it is even more unsatisfactory, since, except in the rare cases of sarcoma starting in a wound, we must suppose the parasites conveyed to the seat of the tumour by the blood, and if this were the case we should expect multiple primary growths to be common.

Carcinoma differs markedly from parasitic diseases in the almost absolute natural immunity possessed by children. To no parasitic disease is there such an absolute natural immunity at any particular period of life as there is to carcinoma during the first two decades. Brault[22] finds an objection to this theory in the fact that in malignant tumours the cells contain large quantities of glycogen, while in the cells resulting from parasitic irritation there is none. In the coccidium nodules in a rabbit's liver the glycogen is situated, not in the epithelial cells, but in the parasites themselves. Another important objection is the fact that it cannot by any possibility explain the origin of congenital sarcomata, and especially those tumours which I have called blastomata. In the case of tumours associated with the presence of

[22] Loc. cit.

bilharzia ova we find that the ova are not the immediate cause of the tumour, but are only remote causes since they are found, not in the tumour itself, but in the neighbourhood. Finally, there is the important fact that all the phenomena of malignant and other tumours can be explained on other grounds—namely, on the view that the cells take on an independent mode of growth and behave as parasites themselves.

We thus see that while the grounds on which this theory is based are inadequate the theory itself will not explain any of the phenomena of malignant disease. We are therefore justified in saying that malignant growths are not to be explained on the assumption of special extrinsic causal factors. It is equally impossible to explain the occurrence of tissue tumours on the parasitic theory, although, as I have shown, if these tumours are due to extrinsic causal factors, these factors must necessarily be of the nature of parasites But it will be said that extrinsic factors are not necessary to explain simple tumours ; to this I answer that there is no justification for separating the tissue tumours from the cell tumours so as to say that, while the one are due to intrinsic factors alone, extrinsic factors are necessary to explain the others. The common factor, therefore, in tumour formation is not to be found in the extrinsic causal agents.

Intrinsic Causes.

We have next to consider the intrinsic factors concerned in the causation of tumours, that is, the factors which arise within the organism at the seat of origin of the tumour. Thiersch, in 1865, called attention to the fact that in old age the connective tissue of the body undergoes atrophy and in consequence becomes unable to withstand the ingrowth of the more active cutaneous epithelium, and to this fact he attributed the origin of cutaneous carcinoma. Cohnheim, who attempted to find the common factor in tumour formation in the rudiment from which the tumour springs, made use of this observation of Thiersch to illustrate his views on the nature of malignancy. According to this author malignancy depends, not on any structural peculiarity of the tumour itself, but on a diminution of the physiological resistance of the surrounding tissues which enables the tumour cells to penetrate into and to destroy them. This diminution of the physiological resistance might be caused by an antecedent inflammatory condition or by the atrophy consequent on old age, or it might be inherited. Woodhead,[23] in his Morton Lecture delivered before this College in 1892, showed sections of the tongue at different ages in confirmation of Thiersch's observations. These showed that the subepithelial connective tissue, which in the young is relatively

[23] The Lancet, May 7th, 1892, p. 1018.

abundant, continually decreases with the increase of age, while the overlying epithelium continues active, so that in old age there is a tendency for the epithelium to send down processes into the subjacent tissues.

We come now to the consideration of Ribbert's [24] theory. This author holds that the tissues in the normal condition are prevented from over-stepping their natural bounds by the action of the "tissue tension" of the part; if this tissue tension is diminished proliferation is set free and a tumour results. This tissue tension represents the sum of the physiological forces acting on the part and is equivalent to the physiological resistance of Cohnheim. According to Ribbert a tumour arises from a collection of cells or a piece of tissue which has become separated from its organic connexion with the surrounding parts and, in consequence, is not subject to the restraining action of the influence of the surrounding tissues; the rudiment is therefore free to proliferate and this proliferation results in the formation of a tumour. The separation of the rudiment may be effected by three means: (1) it may be separated by irregularities in the course of development; (2) it may be the result of trauma; and (3) it may be caused by inflammatory changes in the surrounding tissues. For instance, he explains the origin of carcinoma of the skin as follows. The earliest change is of an inflammatory nature, resulting in a new formation of connective tissue between the epithelium and the cutis vera; this new-formed tissue grows into the superjacent epithelium and isolates either single cells or groups of cells; these cells, being freed from their organic connexion with the rest of the epithelium, are released from the tissue tension of the part and therefore undergo proliferation, penetrating into the subjacent connective tissue and thus giving rise to a carcinoma. The new-formed tissue may be abundant or minimal in amount, but it is never absent. This theory of the causation of tumours is undoubtedly the most satisfactory one that we have yet considered and it possesses the merit of endeavouring to find a cause which shall satisfy the requirements of logic. It is available for the explanation of all tumours and of other conditions such as hypertrophy. I do not agree with Ribbert in assigning so great a part to the connective tissue in tumour causation. The difficulty of deciding this point is great because it is seldom that one examines a carcinoma in a sufficiently early stage, and it is impossible in many cases to say whether the changes observed in any particular specimen would have given rise to a carcinoma if it had been allowed to continue growing.

A theory which is closely allied to that of Ribbert is that which ascribes the origin of a tumour to the loss of nervous control over the cells of which it is composed. The tumour, not being under the control of the central nervous system,

[24] Allgemeine Pathologie, 1901.

grows in an irregular and purposeless manner. This theory was supported by Marshall [25] in his Morton Lecture. The difference between this theory and that of Ribbert lies in the fact that, while Ribbert ascribes the origin of a tumour to the separation of its rudiment from the organic connexion with the surrounding parts, this theory ascribes it to the loss of nervous control. There is no proof that this loss of nervous control can give rise to tumour formation, but, on the contrary, there is ample evidence that it does not necessarily do so, as, for example, in skin-grafting. Beatson [26] suggests that carcinoma of the breast is due, in some way or other, to the influence of the ovaries. There is no evidence in favour of this idea except the fact that certain cases of carcinoma of the breast improve when the ovaries are removed. This fact, however, is not sufficient to form a groundwork of a theory of the origin of carcinoma, since the removal of the ovaries causes profound alterations in the metabolism of the body at large.

Adami's Theory.

Recently Professor Adami [27] of Montreal delivered an address before the Yale University Medical Alumni Association in which he made known his views on the causation of cancerous and other new growths. It is difficult to give in a few words a *résumé* of this most interesting address and I must refer you for the details to the original. Professor Adami agrees, to a certain extent, with Ribbert that the initiation of a tumour is due to the alteration of the tissue tension, but he also admits the action of prolonged stimulation if at the same time the cells are in some way or other prevented from performing their specific function. Proliferation once started will continue as long as the primary modification of physical relationships or the primary stimulus continues to act, if there is adequate nutriment, and if the tensions acting on the cells do not become excessive. The longer the cells are diverted from the performance of their special functions to proliferative activity the greater the tendency for them to acquire permanently the "habit of growth"—that is, the power of proliferation independent of extrinsic conditions, and we thus obtain the purposeless cell-growth characteristic of a tumour.

Now, although I agree with Professor Adami's views to a large extent, yet there are a few points in his reasoning which, to my mind, are not quite satisfactory. In the first place, he states that the controlling agency in the higher katabolic activities of the cell, both functional and proliferative, is the nucleus. In this statement he altogether ignores the centrosome which, as we have seen,

[25] The Lancet, Nov. 23rd, 1889, p. 1045.
[26] Brit. Med. Jour., vol. i., 1899.
[27] Loc. cit.

plays the leading part in the division of the nucleus and the cell. In the next place, he states that proliferation and the active performance of specific function are to a large extent incompatible owing to the different structure of the nucleus under these two conditions, and he argues from this that proliferation can only take place when the cell is unable fully to utilise the assimilated material in the performance of its specific function. I think, however, that in most cases we are equally justified, if not far more justified, in saying that the cell does not perform its function because it is undergoing division. He does not give any reason for supposing that the cessation of function precedes division, and it certainly seems more natural to suppose that the reverse is really the case and that the cell ceases to functionate because it is dividing. It is also impossible in many cases to draw a sharp distinction between the performance of function and proliferation, since in some cases the two are identical. Another defect in this theory is the fact that it does not explain the penetration of the epithelial cells into the surrounding tissues which constitutes the essential lesion in carcinoma. Nowhere in his address does Professor Adami refer to this penetration, but he seems to regard proliferation as the characteristic feature of carcinoma. We may, however, have any amount of cell proliferation without carcinoma, and, indeed, until penetration is present, we cannot be certain that we are dealing with carcinoma at all. Nothing that merely explains the presence of proliferation without at the same time explaining penetration can be satisfactory in affording an explanation of carcinoma.

LECTURE III.

Delivered on Feb. 14th.

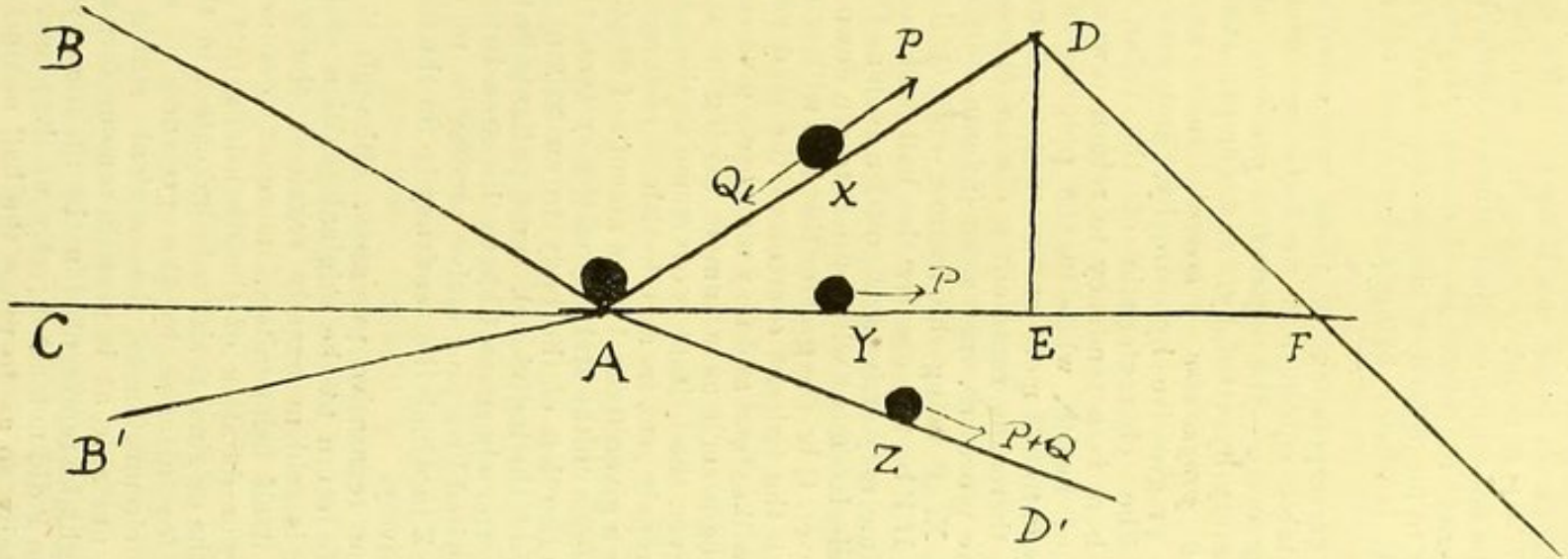
MR. PRESIDENT AND GENTLEMEN,—In the preceding lectures I have considered the classification and life-history of tumours, and I have reviewed various theories which have been advanced to explain their causation. I now propose to consider the relation of tumour formation to other pathological processes.

PHYSIOLOGICAL EQUILIBRIUM.

The various parts of which the organism is composed are normally in a condition of equilibrium; that is to say, each component exists in such a position and quantity as is best suited for the useful performance of its functions, and the functions themselves are also in equilibrium. The position of equilibrium—that is, the exact relation between the component parts—varies in different individuals and in the same individual at different ages. This condition of equilibrium we call *health*. If this condition of equilibrium is disturbed in any way by an alteration in the position, quantity, or function we have the condition known as *disease*. We can represent this by a mechanical illustration (Fig. 1).

Let B A C, D A E, be two inclined planes, the angles at A being equal and the inclinations of the planes being in opposite directions. Let D F E be a third plane sloping from D in the opposite direction to D A. A position of equilibrium—that is, a condition of health—is represented by a ball resting on the planes at A, all forces acting on the ball being supposed to act in the plane of the paper, which is considered vertical. The condition of disease will be represented by a displacement of the ball up the plane A D to a position X, in which it is no longer in equilibrium. At X the ball is acted upon by two forces (neglecting the resistance of the plane), the disturbing force P acting up the plane, which represents the extrinsic cause of the disease, and the component of gravity Q (= W sin D A E, W being the weight of the ball), acting down the plane, which represents the tendency to repair. The stability of the equilibrium is measured by the force Q, and, since this is equal to W sin D A E, it is proportional to the sine of the angle D A E. If this angle is positive—that is, if the planes are above the horizontal line C A E—Q acts in the direction down the plane towards A. If the angle D A E is zero—that is, if the planes are in the position of the

FIG. 1.



horizontal line—Q = O and the condition is one of neutral equilibrium in which there is no tendency to return towards the original position A. If the angle is negative—that is, if the planes are below the horizontal line in the positions A B′, A D′—Q is negative and acts in the same direction as P, and the condition of equilibrium is unstable, there being no tendency to return to the original position A but a tendency to move farther and farther away from that position, this tendency being independent of the disturbing force P.

Now, corresponding to these two conditions of stable and unstable equilibrium we have two groups of pathological processes—the *reparative processes*, such as repair, compensatory hypertrophy, and compensatory hyperergia; and the *progressive processes*, such as tumour formation, progressive hypertrophy, and progressive hyperergia. The characteristic of the reparative processes is that there is a tendency to return towards the original position of health, while in the progressive processes the tendency is to fall more and more away from that position. We can, therefore, represent a disease characterised by the reparative processes, such as an inflammatory disease, by the position X, P being the irritant and Q the tendency to repair. If P be the greater the ball will ascend the plane and in time may arrive at a position such as D, in which any further displacement will cause it to run down the plane D F. If, however, Q be the greater the ball will return towards A. That is, if the irritant overcomes the tendency to repair the disease will extend and may ultimately give rise to a progressive process such as a tumour arising in a chronic ulcer. If, however, the irritant is overcome by the process of inflammation repair sets in and health is restored. It is obvious that, for a given force P, the amount of displacement of the ball depends on the stability of the system, and in the same way the reaction of the body to an irritant depends on the stability of the individual, some patients being immune and others extremely susceptible to the same irritant. A disease characterised by a progressive process is represented by the position Z in which the tendency is for the disease to extend progressively.

In the reparative processes, although the tendency is always to return to the original position of health, yet this position is seldom exactly regained, the position of equilibrium itself being altered more or less according to the intensity or duration of the disturbing factor. This alteration of the original position is indicated, in the healing of a wound for instance, by the presence of a scar. Under certain circumstances the original stable position may become unstable, as is seen in tumour formation in a scar. This might be represented in the diagram by supposing that the force P did not act directly up the plane, but acted more horizontally so as to press the ball against the plane and thereby to depress the latter so as to bring it eventually into

the position A D′. The diagram also shows that under stable conditions the disease will extend so long as the extrinsic force P continues to act, while in the unstable condition the extent does not depend on the extrinsic force but only on the intrinsic.

Now this condition of equilibrium exists between different parts of the body. Firstly, there is a condition of equilibrium between the component parts of the various tissues, that is, between the cells and intercellular substance. If the condition is stable and is disturbed—e.g., by injuring the tissue—the cells at first proliferate out of proportion to the intercellular substance; these cells then lay down the intercellular substance and thus restore the equilibrium, any excess which may occur being subsequently absorbed. This is seen in the *repair* of a wound or a fracture. If, however, the condition is unstable, the cells proliferate continuously without forming the necessary amount of intercellular substance, thus forming a *sarcoma*.

Secondly, there is a condition of equilibrium between epithelium and connective tissue with regard to position. If the condition is stable and is disturbed—e.g., by introducing some epithelium into the connective tissue—the epithelial cells may proliferate for a time but are eventually absorbed or encapsulated. If, for example, a few epithelial cells be introduced into the subjacent tissue, as sometimes occurs as a result of trauma, the effect is that the cells proliferate for a time, forming a globular mass of cells or an *implantation pearl*. If a larger portion of epithelium, including the basement membrane, be introduced, the result is an *implantation cyst*. An implantation cyst is the result of the natural tendency of epithelial cells to cover any bare surface. The cells on each side of the included portion proliferate until they line the cavity in which it lies and the cyst subsequently increases in size only by accumulation of its contents. The implantation cyst, therefore, is not a tumour in the strict sense of the word, since the increase in size is not due to an active proliferation of its cells so much as to the retention of its contents. If the original condition between the epithelium and the subjacent tissue is unstable the epithelial cells which are introduced continue to undergo active proliferation and the result is the formation of a *carcinoma*.

In the next place, there is a condition of equilibrium between the different parts of a tissue forming part of an organ. In stable equilibrium the removal of a portion of tissue leads to a proliferation of the neighbouring portions which continues until the deficiency is made good and then ceases—*regeneration*. Corresponding to this in the unstable condition we have a *tissue tumour* which consists of an overgrowth of a limited portion of tissue.

Again, there is a condition of equilibrium between the amount of the essential tissue and that of the supporting tissue of an organ. In the stable condition atrophy of the essential tissue leads to an increase of the supporting tissue

as is seen in *replacement fibrosis*. The corresponding progressive process to this would be *progressive fibrosis* such as is seen in the fibrosis of nerves, and, possibly, in some forms of cirrhosis of the liver.

Next, there is a condition of equilibrium between the structure of a tissue and the function which it has to perform, both in quantity and quality. In the stable condition any increase of function leads to a corresponding hypertrophy of the tissue; this is *secondary compensatory hypertrophy*. I call it secondary because the primary change in the tissue in this case is hyperergia; examples are seen in muscles and glands. If the function which a tissue has to perform be altered in character the structure of the tissue also undergoes a change to enable it to fulfil its new function. This is *compensatory metaplasia*. If, for example, a surface covered by columnar epithelium is exposed to friction the epithelium undergoes metaplasia and is changed into stratified squamous epithelium. If, again, a tendon, the structure of which is only adapted to withstand a tension in the direction of its fibres, is called upon to support a stress at right angles to that direction, its structure becomes modified by the formation in it of cartilage or bone. Examples of this are found in sesamoid bones, drill bones, &c. The corresponding process in the unstable condition is *progressive metaplasia* such as is seen in myositis ossificans.

In the next place, there is a condition of equilibrium between the size of the different organs. If the equilibrium is stable and is disturbed by removing a portion of an organ or one of a pair of organs, the remaining portion undergoes *compensatory hypertrophy*. Whether or not a true primary compensatory hypertrophy, as distinct from the secondary form, exists, seems to be a matter of doubt—at any rate after intra-uterine life. The corresponding process in the unstable condition is *progressive hypertrophy*, examples of which condition are seen in the prostate, breast, thyroid gland (goitre), bones (leontiasis ossea), and perhaps in the lymphatic glands in Hodgkin's disease. The hypertrophy in these cases is not accompanied by hyperergia.

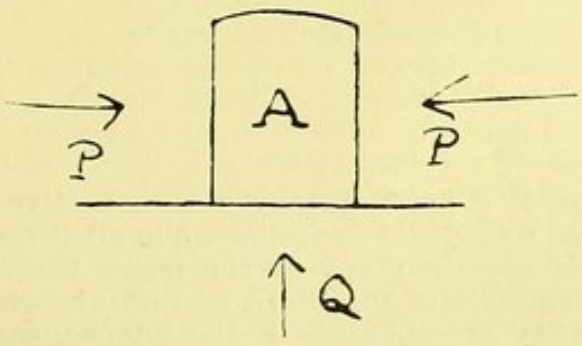
Lastly, there is a condition of equilibrium between the functions of the different organs. Diminution of the function of an organ leads to *compensatory hyperergia* of a similar or correlated organ. Corresponding to this we have, in the unstable condition, *progressive hyperergia*, examples of which are found in the kidneys (diabetes insipidus), leucocyte-forming organs (leucocythæmia), and, perhaps, in the thyroid gland in Graves's disease. Hyperergia, whether compensatory or progressive, is followed by secondary compensatory hypertrophy.

We see from the foregoing considerations that diseases may be divided into two great classes: (1) those which occur in a body in which the condition of equilibrium is stable; and (2) those which occur in a body in which the equilibrium is unstable. The pathological processes which

characterise the diseases of the first class all tend towards the restoration of the original position of equilibrium, while those which are characteristic of the diseases of the second class have a progressive tendency away from the original position.

I have omitted all mention of the retrogressive processes, but on examining these we find that, in the same way, some are characteristic of stable, others of unstable equilibrium. The former are due to definite causal factors which are extrinsic to the part concerned ; they cease on the removal of this factor and restoration takes place. The latter are not characterised by definite extrinsic factors and restoration does not occur. We can, in fact, liken the organism, the cells, tissues, and organs of which are in stable equilibrium to a nation composed of individuals bound together by a well-ordered government and various moral forces, and living together in harmony and prosperity, each individual doing his own work and propagating his own species. In such a community if an attack were threatened from without those at the point attacked would first resist the invaders and if these were unsuccessful the whole number of individuals would take their share in defence. On the other hand, an organism, the component parts of which are in unstable equilibrium, can be likened to a nation of individuals discontented with the government and at variance with each other. In such a case a very slight attack from without would suffice to kindle a rebellion on the part of the discontented faction which would tend towards the destruction of the nation. The same effect might easily occur, without any extrinsic interference, from intrinsic causes alone. Thus the reparative processes constitute a defence of the organism against extrinsic injurious agents, while the progressive processes constitute a rebellion on the part of certain components against the mastery of the body as a whole. What, then, are the forces between which this equilibrium exists? We can represent them diagrammatically in the following way :

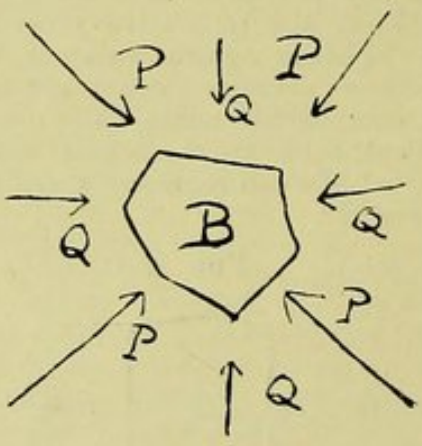
FIG. 2.



Let A (Fig. 2) represent an epithelial cell. This cell possesses an intrinsic tendency to proliferate in all

directions. This tendency is kept in check by certain forces P exerted by the epithelial cells adjacent to it and by the force Q exerted by the subjacent connective tissue. Under normal conditions the tendency to proliferate and these intercellular forces are in equilibrium. As the tendency to proliferate in the direction of the free surface is not counteracted by any intercellular force proliferation may take place in this direction. In the case of secreting cells, however, proliferation towards the free surface is replaced by secretion. If, now, we remove one of the forces P, as by removing the neighbouring epithelial cells, proliferation is set free in the direction of the removed force. The same will be the case if one of the forces P be diminished instead of being removed, as is the case in the epithelial cells lining a retention cyst. If the original condition of equilibrium was stable the force P will be restored by the proliferation and the equilibrium will be regained. This is the case in regeneration of epithelium following a wound, &c. If, however, the equilibrium was originally unstable the force P will not be restored and proliferation will continue, thus giving rise to an epithelial histioma. If the force Q be removed or diminished proliferation will take place into the subjacent connective tissue. In this case. if the original condition was stable, the force Q would be restored and proliferation would cease. If, however, the equilibrium was unstable, the force Q would not be restored and proliferation would continue in the connective tissue giving rise to a carcinoma.

FIG. 3.



Again, let B (Fig. 3) represent a connective tissue cell. This cell has a tendency to proliferate in all directions, which tendency is kept in check by the forces P exerted by the neighbouring cells of the tissue, and also by certain forces Q representing the influence of the intercellular substance. If the forces P are diminished or removed, the forces Q remaining the same, proliferation will take place and will be accompanied by the formation of the normal amount of

intercellular substance. This will give rise, in the stable condition, to regeneration of the tissue ; in the unstable, to a histioma consisting of the same kind of tissue. If, on the other hand, the forces Q be diminished, proliferation of the cells will occur, but the intercellular substance will not be formed in the proper amount and this will give rise in the unstable condition to a sarcoma and, in the stable condition, it is seen in the proliferation which is characteristic of repair. The other processes to which I have referred might be represented in a somewhat similar manner.

As to the nature of these intercellular forces we have no knowledge. They are apparently not the recognised physico-chemical forces nor are they nervous, although the nervous system may have an effect in regulating them. Development proceeds regularly and uniformly under the influence of these forces before the existence of nervous connexions, the different tissues developing in their proper situations and of their proper structure according to the part which they have to play in the organism. The more we study the growth and development of living organisms, the more difficult it is to believe that vital phenomena can be explained on a physico-chemical basis. The intercellular forces may be altered directly by extrinsic agents such as irritants, but, being intrinsic forces, they may also be affected by intrinsic factors without the direct action of external agents.

Causation in General.

A cause is defined by logicians as the invariable, unconditional antecedent of an event which, in relation to the cause, is called the effect. A cause is said to have five characteristics : it is quantitatively equal to the effect and qualitatively it is invariable, unconditional, immediate, and antecedent. Cause, in this sense, is the sum of all the conditions which are necessary for the occurrence of the event. A cause, it is to be noticed, is not a definite entity, but is a state or process ; it is essentially matter in motion. The equality of cause and effect follows from the principles of the conservation of energy and the indestructibility of matter. The effect is, in fact, the cause redistributed ; hence it follows that any substance which forms part of the cause must also be found, in some form or other, in the effect. For any given event there is only one cause and a given cause gives rise to only one effect. We can, however, consider the cause itself as an effect and proceed to inquire into its causation. We thus arrive at intermediate and remote causes, but the farther we proceed the more conditions we introduce. We can thus divide causes into immediate and remote, the remote being connected with the immediate by a series of intermediate causes. Of these the only unconditional cause is that which is immediate, remote causes being always conditional. In the remote causes there are, however, certain essential factors present.

To take an example, let us consider tuberculosis. This disease is defined at the present day as a disease caused by the bacillus tuberculosis, and the only certain method by which we can say that a given disease is tuberculosis is to demonstrate the presence of the bacillus. The immediate cause is therefore the action of the bacillus on the living tissues. If we proceed a step farther and inquire into the cause of this action we find that it is the entrance of the bacillus into the tissues with the condition that the tissues must be capable of being acted upon by the bacillus, or, in other words, that the tissues must be susceptible. We can proceed step by step in the same way and arrive at more remote causes, but however remote the cause there must always be present the essential factor—namely, the bacillus itself. Tuberculosis is therefore a disease characterised by an essential causal factor which is of extrinsic origin.

To take another example, let us consider carcinoma. The characteristic feature in carcinoma is the presence of proliferating epithelial cells in the connective tissue spaces. In carcinoma, therefore, there is no necessary extrinsic factor present corresponding to the bacillus of tuberculosis and, from the equality of cause and effect, there can be no necessary extrinsic factor in the cause of carcinoma. The immediate cause of carcinoma is the disturbance of an unstable position of equilibrium between the epithelial cells and the connective tissue so that the epithelial cells penetrate into, and proliferate in, the connective tissue, the essential factor—namely, the instability—being intrinsic. The immediate cause of carcinoma is, therefore, an intrinsic one and involves no extrinsic factor.

Etiology of Tumours.

In considering the causation of tumour formation we must take into consideration the peculiarities of tumours. In the first place, tumours are local overgrowths, and in the second, this overgrowth is progressive—that is, it is not limited by the influence of the surrounding tissues. Now the growth in tumours does not differ essentially from that of normal structures and there is no reason to suppose that the cause of the proliferation is different in the two cases. Cell division is, as Adami states, an intrinsic property of the cell and is only influenced indirectly by extracellular conditions. The usual conditions which give rise to proliferation are injury or removal of the neighbouring cells, thus producing an alteration of the intercellular forces acting on the cell. Increased functional activity and increased blood-supply also give rise to proliferation. In addition, these intercellular forces may be altered by intrinsic conditions.

The progressive nature of the growth in tumours shows that the original condition of equilibrium of the part in which the tumour arose was unstable, so that the growth,

once started, is not opposed by the normal intercellular forces. This instability is the determining factor of tumour formation and the other progressive processes, as in its absence no amount of extrinsic irritation would give rise to them. In this instability of equilibrium, then, we have found that for which we have been seeking, namely, the common factor of tumour formation. The cause, then, of the progressive processes is the disturbance of a part of the body the component elements of which are in unstable equilibrium. This satisfies the necessary qualitative conditions of a cause ; it is immediate, unconditional, invariable, and antecedent, and it is the only cause which satisfies these conditions, any remoter cause being conditional. If we proceed to look for the causes of this instability—that is, for the remote causes of tumour formation, &c.—we find that they are many and of various kinds. They may be the same as those which cause the disturbance of the equilibrium or they may be different. Chronic irritation is a frequent cause ; this may be mechanical, as in the irritation of a tooth or as in soot and paraffin cancer, or it may be parasitic, as in the carcinoma arising in lupus nodules, and in the bladder tumours which are sometimes met with in bilharzia disease. Dr. T. Harris[28] of Manchester has described a case of carcinoma associated with bilharzia irritation, in which the ova were found, not in the tumour itself, but in the tissues of the bladder wall in the neighbourhood. The ova had given rise to a chronic irritation which had produced a condition of unstable equilibrium with the formation of a tumour as a result. Besides these extrinsic causes, which, it will be observed, have no specific characters, there are also intrinsic causes. The great frequency with which the female organs of generation are the seats of tumour formation is to be explained by the frequent alternations of rest and activity to which these organs are subject. Tumours have often been attributed to mental worry and similar conditions, and Sir William Bennett, in the lecture to which I have previously referred, described two cases in which mental concentration directed to the breast seemed undoubtedly to have taken part in the causation of tumours in that situation. Age also plays a part especially in the causation of carcinoma, and the observations of Thiersch, Woodhead, and others have shown that it acts through the relative atrophy of the connective tissue compared with the more active epithelium.

The influence of heredity on the causation of tumours has been variously estimated and I do not propose to go into the statistics on this point. There can, I think, be no doubt that heredity has a share in causation, but it is not the tumour, but the unstable condition of equilibrium, which is inherited. The extent to which the body cells proliferate in

[28] Transactions of the Pathological Society of London, vol. xxxix., 1888.

normal development and growth is undoubtedly inherited and, since errors of development are admitted to be inherited to a certain extent, it is probable that errors of growth, such as tumour formation, may be also. Tumours, however, may be congenital without being inherited and are, in this case, apparently due to a defect in the normal heredity of structure. Just as there may be a defective development of an organ, so there may be a defective development of the intercellular forces. The part which heredity plays in tumour causation differs from the part that it plays in the causation of such diseases as tuberculosis in the fact that in tumours the essential factor—namely, the unstable condition of equilibrium—may be inherited, while in tuberculosis it is the adjuvant factor, the susceptibility, which is transmitted.

An important factor in tumour causation is to be found in the influence of civilisation. Cancer is admittedly more common among civilised nations than among uncivilised, and it is more common among domestic animals than among those that are wild. Civilisation acts probably by means of the unnatural mode of life which it entails. Indoor life, sedentary occupations, excessive feeding, unnatural clothing, the mental worry and excitement which are inseparable from such a life all play their part. It is to these factors that we must look for an explanation of the alleged increased frequency of cancer at the present day.

It is not to be supposed that the equilibrium throughout the body is in an unstable condition. The instability sometimes affects the whole of one tissue in an organ, as in the case of diffuse sarcoma and carcinoma, but it is usually limited to a much smaller area, to a minute piece of tissue or even to a single cell or group of cells. While, then, this instability explains the occurrence of the primary tumour, it will not explain its extension to surrounding parts nor will it explain the occurrence of metastasis.

There are certain bacteria which at first grow with great difficulty on artificial media; by frequent transplantation, however, they acquire the property of growing readily on such media and this property is transmitted to their descendants. In the same way the cells of a tumour by continuous proliferation in the primary growth acquire an increased power of proliferation which power is handed on to their descendants. If, then, these descendants arrive in a region in which the equilibrium is stable, they are able to proliferate in spite of the resistance offered to them and so to give rise to tumour growth. This increased power of proliferation is called by Adami the habit of growth. Once the cells have acquired this habit they behave as independent parasites. This explanation of malignant disease—namely, that the cells themselves act as parasites—will explain how it is that tumours are, as a rule, only infective among animals of the same species, since it is known that the blood of an animal can be replaced by that of another animal of the same species, but not by that of an animal of a different species;

transplantation of tissues, also, is only successful between animals of the same species.

As I have mentioned previously, the wasting and cachexia of malignant disease can probably be explained by the destruction of tissue and the drain of nutriment by which it is accompanied, especially by the loss of carbohydrate material. Absorption of the products of degeneration may also take part in the causation of these conditions. This view of the pathology of tumour formation is based on the groundwork of observed facts and will explain all the phenomena associated with tumour growth.

Summary of Conclusions.

I would sum up my conclusions as to the pathology of tumour formation as follows : 1. Tumours are to be classified on a histological basis. The best mode of effecting this is to make use of the three-fold basis of cells, tissues, and organs. 2. The rudiment from which a tumour springs may consist (1) of the structures normally present at the point of origin ; (2) of an embryonic collection of cells such as is described by Cohnheim ; or (3) of tissues of new formation, the result either of an inflammatory condition or of previous tumour formation. 3. Extrinsic factors play a part in tumour causation, but are not the determining factors—that is, the occurrence or non-occurrence of a tumour does not depend on extrinsic factors. In particular, the parasitic theory is shown not to stand a critical investigation. 4. The determining factor in tumour causation is to be found in the intrinsic factors. 5. This determining factor consists in the existence of a condition of unstable equilibrium between the intercellular forces, so that proliferation, once started, is progressive and is not limited by the resistance of the surrounding tissues. 6. The causes of this instability are many and various and may be either intrinsic or extrinsic. 7. Proliferation having started, the cells acquire the habit of growth—that is, the power of independent proliferation which enables them to proliferate in parts of the body in which the condition of equilibrium is stable. 8. Tumours grow by proliferation of their own cells. 9. Tumours do not invariably continue to increase without limit. Under certain circumstances they may cease to grow and may diminish in size or may even disappear completely. 10. Tumour formation is not to be regarded as an isolated process but is to be considered as one of a group of progressive processes with which it is closely allied. Still less must one form of tumour, such as carcinoma, be considered apart from the others.

Indications as to Treatment.

It is not my duty as a pathologist to enter into details regarding the treatment of tumours, but we must remember

that the three divisions of practical medicine and surgery—namely, pathology, clinical observation, and therapeutics—are mutually interdependent. The pathologist learns much from the clinician and the therapeutist and in return can render them assistance by suggesting modes of treatment. It is one of the most important duties of pathology to point the way to new methods of diagnosis, prognosis, and treatment, and without this it would have no practical utility.

If we refer to our mechanical illustration (Fig. 1) we see that when the ball has been displaced to the position X it can be brought back to its original position by two methods—either by removing or diminishing the extrinsic force P or by increasing the force Q. Since the force Q depends on the angle D A E, we can increase the force Q by increasing this angle. Similarly in disease we can either remove the extrinsic causes or we can increase the resistance of the body so as to enable it to overcome these causes. We can also act upon any intrinsic factor that may intervene between the extrinsic cause and the ultimate effect. In the case of tumours and the progressive processes generally, since we have to do with an active cellular proliferation we can hinder this by diminishing the supply of nutriment.

I have pointed out that the extrinsic factors in tumour causation are many and various and that they only act in initiating the disease. The removal of these factors, therefore, will act mainly as a prophylactic. For this purpose all sources of irritation, whether mechanical, parasitic, chemical, or the result of inflammatory conditions should be removed or avoided, especially in the case of those who show a propensity to tumour formation, such as those from whom a tumour has already been removed. This mode of treatment has, obviously, only a limited application. By removing the tumour we remove at once the area in which the condition of equilibrium was unstable and the cells which have acquired the habit of growth. In the case of simple tumours this mode of treatment will effect a permanent cure, and the same will be the case with a primary malignant growth if the removal is complete—that is, if all the cells which are the result of the tumour growth are removed so that none are left to find their way to distant parts of the body to give rise to metastatic tumours. This method of treatment is, and will remain, by far the most important, both with simple and malignant tumours. Unfortunately, it is not common to meet with malignant growths in a sufficiently early stage to enable us to be certain of effecting their complete removal, and after removal it is practically impossible, even after a minute histological examination, to be quite sure that all the proliferating cells have been removed.

Seeing that proliferation of cells plays the important part in tumour formation, it is natural to ask whether it is possible to hinder the proliferation by any process of starvation. Starvation might be induced, either by a

general reduction of the nutriment supplied to the body, or by a local cutting off of the nutriment such as is effected by ligature of the arteries which supply the tumour with blood. We should not expect much from the first method, since the other tissues would be equally affected by the deficiency of nutriment. The second method has been tried in some cases of inoperable carcinoma with the effect of temporarily diminishing the rate of growth.

I have previously referred to the presence of large quantities of glycogen in tumours, especially in those which are malignant. This glycogen is found wherever active proliferation is taking place and it supplies the energy necessary for the proliferation. The question arises, therefore, whether we can control this supply in any way. In glycosuria we know that the carbohydrates excreted in the urine may be derived either from the ingested carbohydrates or from the proteids of the body. The origin of the glycogen in tumours has not been investigated so fully, but probably the same two sources are available as in diabetes. An examination of the quantity of nitrogen excreted in the urine would be of assistance in determining this point, but I am not aware of any systematic investigations in this direction. The urine in malignant disease has not received the attention that it deserves. The presence of wasting and cachexia would seem to show that the proteids of the body are broken up and it is very likely that the glycogen arises, in part at least, from this destruction of proteid matter. If this is the case we cannot expect much from a carbohydrate-free diet, since the body proteids would still remain as a source of the glycogen. Is it possible, then, to remove the glycogen which has been formed? We know that malignant disease is very rarely met with in association with diabetes, and we also know that in acute diabetes wounds heal with great difficulty. The explanation of this is probably that the glycogen which is necessary for the proliferation of cells is continuously being removed from the body as glucose. It is permissible, then, to think that by setting up an artificial glycosuria we could remove the glycogen as fast as it is formed and so prevent it being available for supplying the energy necessary for the proliferation of the tumour cells. Such a glycosuria may be set up by means of certain drugs—such as phloridzin. This is a point which might well be investigated by therapeutists. I am afraid, however, that we must not expect much from such a treatment because the drug would remove the glycogen from the normal tissues as well as from the abnormal, and it would be of little use to hinder the progress of a tumour if the surrounding tissues were not able to take advantage of the occasion by reacting and absorbing it. Much depends on the question whether the normal or the abnormal tissues would yield up their glycogen most readily.

The most important question at the present time with

regard to malignant disease is whether anything can be done to prevent or to retard recurrence and metastasis and to benefit inoperable cases. As I have pointed out, tumours are essentially due to intrinsic causal factors, and any treatment should, therefore, be directed towards these factors. The cases described by Sir William Bennett, to which I have referred, and numerous other recorded cases, show that malignant disease does not always proceed to a fatal termination but may become arrested and even cured. To facilitate this course measures should be taken which would raise the enfeebled resistance of the body tissues. In this connexion I may mention that arsenic, which has a markedly tonic action, has been recommended in all diseases characterised by the progressive processes and in some cases with some degree of success. At a recent meeting of the French Académie de Médecine Dr. Lucien le Roy [29] gave an account of a case of cancer of the lung in which the patient apparently recovered after treatment with arsenic and quinine. The details of this case are not yet published. Coley's fluid probably acts in the same way by producing an increased reaction of the surrounding tissue against the tumour and the same may, perhaps, be said of such procedures as oöphorectomy and feeding with thyroid extract. This last mode of treatment has been recently reviewed by Mr. H. T. Butlin [30] who comes to the conclusion that the benefit derived from it is only temporary.

The immense improvement which has taken place in the treatment of tuberculosis points the way to a similar procedure in malignant disease. This hygienic treatment acts by increasing the resistance of the body tissues to the encroachments of the tubercle bacilli and I think that it is worth while to consider whether by a similar mode of treatment, the body tissues could be encouraged to resist with greater force the encroachments of the tumour cells. I am inclined to think that if a patient from whom a malignant tumour has been removed, instead of returning to a sedentary and unhealthy mode of life, were to lead an active outdoor existence in a healthy climate with sufficient exercise and good plain food, leading as natural a life as possible, there would be less tendency for the disease to recur, and it is possible that a tumour, already present, might under these circumstances show a slower rate of growth or might even undergo a diminution.

And now, Mr. President and Gentlemen, my task is ended. I have laid before you no new hypothesis, nor have I brought forward any startling experimental results. I have endeavoured to bring to your notice the facts, mostly well known to you, concerning the process of tumour formation and to show what conclusions we can legitimately draw from these facts, and I have tried to point out to what modes of treat-

[29] Brit. Med. Jour., Jan. 25th, 1902.
[30] Ibid., Jan. 4th, 1902.

ment these conclusions lead. Finally, I would urge that the investigation of the pathology of malignant disease should not be left altogether to the bacteriologist. Histologists, pathological chemists, clinicians, and therapeutists should all take part, for much remains to be discovered in all these branches of medical research. There is especially a great field for work in the study of the clinical characters of malignant disease such as the temperature, the urine, and the phenomena of cachexia. There is too much tendency at the present day to regard micro-organisms as everything in the causation of disease and to neglect the personal or intrinsic factors. I would also urge that the investigation should not be confined to the malignant tumours alone, but should include other tumours and those processes which are allied to tumour formation. It is only in this way that we can hope to arrive at any final conclusion as to the pathology of tumour formation.

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