ON THE CLASSIFICATION OF TUMOURS.¹

By J. GEORGE ADAMI, M.A., M.D., *Montreal*.

ONCE it was established by histological studies that the different forms of neoplasms arise from different tissues, it became possible to group tumours according to their origin. Once again, when, through the observations of the embryologists, it was recognised that the tissues could be grouped according to their origin from the primitive cell layers, it became possible to group tumours in the same way. This was done more especially by Waldeyer, and we obtained thus a classification of tumours into those of *mesoblastic* origin and those of *epiblastic* and *hypoblastic* derivation, the tumours derived from the two latter cell layers being grouped together, for it was soon found that they were of the same general type.

Here was a broad and very important generalisation, and, what is more, in the then stage of histological and embryological knowledge, it appeared not only to be founded on a sure and scientific basis, but to fulfil to the fullest the needs of the worker. For it appeared to separate two sharply differentiated orders of tumours—those of connective tissue origin and connective tissue type from those of epithelial and glandular origin and epithelial and glandular type. So that for long years this distinction remained dominant; even to-day, in at least one text-book published during the last twelve months, that by Dr. Nicholas Senn, this is given as the acceptable classification.

It is, however, scarcely necessary to say that, with increasing knowledge, many cases were discovered which did not fit into this scheme. A classification which brings together unlike bodies, making them members of one group, is, on the face of it, inadequate and faulty. Now, more especially during the last ten years, *pari passu* with a recognition of the bearing of the fuller and more recent findings of the embryologists, this classification has been found to have the above failing. It is, for example, generally accepted that the specific and characteristic cells of several tissues of the glandular type—of the kidneys, suprarenal bodies, ovaries, testes, and uterine mucosa—are of mesoblastic origin, but these, nevertheless, give rise

¹ The main body of this paper was contributed as an address to the Toronto Pathological Society, January 4, 1902.

to tumours which may and often do resemble most closely those of hypoblastic and epiblastic origin.

There has been grave doubt as to the embryogeny of the organs in question. The idea that tissues of glandular type can only be derived from the two primary cell layers is very firmly fixed, and in one direction the attempt has been made to show that the organs in question are of hypoblastic or epiblastic origin; on the other, to make out the distinction between these organs and what have been termed "true glands." But I am only expressing the general opinion of modern embryologists and histologists, when I say that all these organs now are accepted by the majority as being definitely derived from mesoblast. And thus the cancer-like tumours which originate in these organs must be accepted as being mesoblastic.

On the other hand, the gliomata have a structure which brings them into close alliance with the atypical or malignant connective tissue tumours, and yet the neuroglia, from which they are derived, is of epiblastic origin. The notochord, again, is an organ of hypoblastic origin. According to Ribbert, and the view is becoming accepted, the remains of this fetal organ may give rise to tumours somewhat resembling myxomata, that is to say, to tumours which, though of hypoblastic origin, are of connective tissue type. Histologically, and for practical purposes, the first series above mentioned ought to be grouped along with the adenomata and carcinomata, and the second with the sarcomata and connective tissue tumours, but the old embryological classification forces us to make the very opposite arrangement.

These difficulties have induced so strong a reaction that one has only to read the recent text-books and articles published during the last ten years to recognise that pathologists in general, nowadays, refuse to consider embryogeny in their schemes of classification, and from Thoma, or even earlier, from Hamilton in 1889,—onwards, through Ribbert and Lubarsch—the list is so long that I need not give it,—the tendency has been to divide the autonomous neoplasms into those of typical and atypical connective tissue appearance, and those of typical and atypical glandular appearance. Some, like Hansemann,¹ would go so far as to declare that tumours must be described purely according to their histological appearance, and while certain terms in general use must continue to be employed,—terms such as adenoma, sarcoma, etc.,—nevertheless the only right classification at the present time must be by the organ, the tumours originating from one or other tissue being grouped together. So that, for example, we must group together the adenomata and carcinomata of the liver as a class distinct from the adenomata and carcinomata of the stomach. In short, they urge that the topographical classification is the only one possible at the present time.

There is undeniably a virtue in this position, provided that it is

¹ Hansemann, D., "*Die mikroskopische Diagnose der bösartigen Geschwülste*," Berlin, 1897, S. 22.

assumed in a proper spirit and regarded in the right light; not as a final stage, beyond which it is impossible to advance, but as a temporary stage of careful collection and collation of all the facts bearing upon the tumours proper to each individual organ, to the end that we may, from the knowledge so gained, proceed to further and sounder generalisations, that we may utilise the facts so amassed, to formulate broad statements concerning neoplasms, their relationship one to the other, and their mode of growth.

But against such a position this has to be said: all these years, whatever the scheme of classification popular at one time or another, pathologists have not been idle, so that we are already in possession of an enormous amount of material, and, what is more, of accurate drawings of the same. Hence, if preconceived notions as to embryological relationships modified the earlier conclusions reached concerning one or other form, the details have been honestly described, and the descriptions and the accompanying illustrations help us to determine where the earlier conclusions need correction. Nay, more, we already possess exhaustive studies upon the various forms of tumours affecting one or other organ, the mammary gland, uterus, kidney, skin, etc. Taking everything into consideration, the time ought to be ripe for attempting more than this individualising method. So, to repeat, I believe that we have by us embryological and anatomical observations, which permit us to proceed further. What is more, I believe that, for a sound classification, we must inevitably pass backwards to the developmental relationship of the different tissues, that we must accept an embryogenetic basis, but one more in consonance with our present knowledge.

It is not necessary here to dwell upon the relationship of morbid to normal processes, and to show that the former in each case are but exaggerations in one or other direction of the latter; nor need I point out the importance of a knowledge of the development of each tissue in arriving at a determination of the modifications which may be undergone by that tissue. In his Middleton-Goldsmith lecture in New York, Minot¹ has during the last year treated this latter subject in so masterly a manner, that anything I could say would be but a feeble reflection of his admirable presentation of the bearing of embryology upon pathology. What I wish now to point out more especially is that we pathologists—and we are not by any means the only ones to blame—have during these years continued to hold fixed and stereotyped views with regard to the exact nature and development of the different germinal layers, and it has been this misconception of these layers and the changes undergone by them, and of the mode in which the various tissues have been derived from them, that has brought us to this stage of discarding classifications constructed along embryological lines.

¹ "On the Embryological Basis of Pathology," *Science*, U.S., 1901, vol. xiii. p. 481.

We have, that is, held as a body, that from a given layer, as, for example, the epiblast, only tissues and tumours of one general type are developed, and in practice we have found that this is not wholly the case. We have concluded that embryogenesis is a broken reed, and this despite our willingness to discover in it the basis for sound classification.

In order to indicate how a classification, which is primarily embryological, can be developed, it will be necessary for me to indicate rapidly what are the leading facts with regard to the earlier stages in the development of the different types of tissue, and I must recapitulate matters of a most elementary nature; nevertheless, if by doing this I can make my argument clear, I trust that I shall be forgiven.

The earliest stage to be recognised in the development of the fertilised ovum, once it has proceeded to segment, is the production of a morula, in which the blastomeres form a cluster or group of cells of the same order, with almost entire lack of differentiation. Rapidly this gives place to a second stage in which the component cells arrange themselves into two layers, the *epiblast* and the *hypoblast*, so that, at a singularly early stage, the future epiderm and endoderm are recognisable. The next stage to be noted is that the hypoblast, or internal of the two primitive layers, gives rise by proliferation of its cells to a group or mass of cells which now lie intermediate between the primitive epiblast and the hypoblast, and form the *Anlage* of the mesoblast and of the organs derived from that layer, the hypoblast itself still remaining as a distinct lining membrane. What I would here note is, that we are perfectly willing to advance thus far and recognise these two primary and the third secondary cell layer. But there, in our appreciation of embryology as bearing upon pathology, we have been strangely apt to stop.

But now, just as the hypoblast gives origin to the mesoblast, so it is perfectly legitimate for us to recognise a similar process on the part of the epiblast; for the epiblastic cells in the immediate neighbourhood of the primitive groove proliferate rapidly, and, in so doing, project in part below the original line of the epiblast, and, being forced inwards, a regular mass of cells is developed, in the central portion of which, around the spinal canal, there still remains evidence of its origin, in the form of a definite epithelial lining. This second portion becomes cut off completely from the superficial epiblast to form the mother tissue of the nervous system. Similarly, the hypoblast gives off a second localised mass of cells to form the notochord.

Professor Minot has called my attention to the fact that, while possessing special features, the cells forming the notochord throughout retain epithelial characters, that they are grouped together without an intercellular matrix, that no vessels penetrate between them, and that, although in degeneration these cells assume a somewhat dubious appearance, they can most assuredly not be regarded (as I find, on reading Hansemann and other recent writers, I had not been alone in regarding them) as assuming a connective tissue type. The nature

of the cells forming the chordoma of Ribbert makes him more than doubtful as to the origin of this form of tumour from notochordal remains. I have thus, in deference to his authority, modified to some extent my original statements regarding this.

The point I wish here to indicate is that mesoblast, "neuroblast," and notochord are derived from the two primitive cell layers, and, the first two, at least, *lose the lining-membrane characteristics of these two earliest layers, and take on a less differentiated condition prior to further evolution.* At a somewhat later period the mesoblast repeats the process of differentiation, and, from being a simple undifferentiated cell mass which we may compare with the morula, certain of its cells growing outwards between the epiblast and hypoblast become arranged into a definite layer, to form or enclose the primitive body cavity. From this point onwards we can distinguish two structures of mesoblastic origin—the *mesothelium*, or lining membrane portion of the mesoblast; and the *mesenchyme*, or, as I may term it, the mesoblastic pulp.

It will be seen that I here make no note of the separation of mesoblastic elements into *archiblast* and *parablast*, as laid down by His, and made the basis for a classification by Klebs and Williams. His's conception of the parablast, as arising from the elements of the white yolk and from the "granulosa cells," is now known to be wrong, and indeed he has himself withdrawn his earlier hypothesis as to its origin. Add to this, that so hopeless a confusion has arisen among writers as to what is archiblastic and what parablastic, that we have no option but to discard these terms. As pointed out by Minot, the recognition of the separation of the mesoblast into mesothelial and mesenchymatous elements respectively, suffices for all practical purposes to indicate that which is of real importance in His's observations, namely, the recognition of the ultimate evolution of the primitive mesoblast into two distinct series of cellular constituents.

For our purpose, it is unnecessary to choose definitely between the two main contending views as to the origin of mesenchyme. Whether all the primitive mesoblast first passes into a mesothelial stage, from which by further proliferation the mesenchyme is derived; or whether, on the other hand, a portion of the mesoblast does not undergo conversion into mesothelium, but continues directly to develop into mesenchyme, is for us a relatively secondary matter. The important point is, that we have to recognise that the primitive mesoblast is eventually separated into these two sets of cells, and of these the mesothelium is differentiated into a layer of the lining membrane type.

At a still later date masses of mesothelial cells again accumulate, and, as was the case with the epiblast and the hypoblast in the earlier stage, they give off on either side a mass of more undifferentiated cells, and these masses form the mother tissue or *Anlage* of the eventual striated muscle. Later, though still in this embryonic period, with the development of the first vessels, the mesenchyme gives off a series of cells of the lining membrane type, which form the eventual lining cells, or endothelium, of the vascular and lymphatic systems.

There is still some little uncertainty as to the exact relationship of the vascular endothelium, whether it be directly derived from mesothelium or from the mesenchyme. As Professor Minot has pointed out to me, His has of late indicated that it is of relatively very early development in certain forms. On the other hand, I learn from Professor M'Bride that relatively

high up among the forms of animal life it may be wanting, as, again, it may only show itself at a period definitely later than the development of the vascular channels. What I have stated above, thus, may be taken as representing, as accurately as is possible at the present time, the generally accepted relationships in time of endothelial to other embryonic developments.

Thus during early embryonic life we obtain a series of differentiations of the primitive cell layers leading to the production of two sets of tissues; one which we may term the *lining membrane tissues*, the other, the *pulp tissues*. I do not wholly like the latter expression, but can think of none other which more nearly expresses the con-

SCHEME OF TISSUE RELATIONSHIPS.

Lepidic tissues.—1, Epiblast (ectoderm and glands); 2, hypoblast (entoderm and glands); 2', notochord (hypoblast); 3, mesothelium (lining body-cavity) with derived glands; 4, endothelium (lining vessels).

Hylic tissues.—5, Epiblastic (forming nervous tissues); 6, mesothelial (forming striated muscles); 7, mesenchyme; 8, pleuro-peritoneal cavity; 9, lumen of alimentary canal.

ception which I wish here to impress on the reader, namely, that in this very earliest stage the mother cells from which certain tissues are derived already have a definite order and position, as constituting membranes, whereas the mother cells of the other group of tissues lack this definite order and exhibit no marked differentiation.

If, now, we follow up these two orders of tissues to their full development, we find that from the lining membranes are developed tissues of one character, from the pulp, tissues of a different character. These lining membranes, from whatever layer they originate, may either remain as functional membranes covering an extensive surface, or they may become modified so as to form the various highly specialised and specific constituents of various organs. To reach this latter stage the epithelium either undergoes extensive infolding, or sends downward tubular processes, which branch to a greater or less extent, or again which sends downward solid processes, as occur, for example, in the development of the suprarenal. In quite a large number of instances it would seem that the first process in the production of the tubular glands is one of budding, or projection downwards into the underlying mesenchyme, of solid processes, which subsequently became hollowed out and tubular (*e.g.* sudoriferous glands and renal tubules). Thus it comes to pass that the various glandular organs are formed of a parenchyma originating from one of the primitive lining membranes and a stroma of connective tissue which is of mesenchymatous origin. And even in cases where there is the widest divergence from the original type of lining membrane, we find that this distinction still holds, that the parenchymatous cells form *layers or groups into which the vessels do not penetrate, and in which there is an absence of stroma between the members of the cell groups*, the cells being at most united by bridges and by a fine cement material. While, contrariwise, regarding tissues originating from the embryonic pulp, we notice that in them the prominent characteristic is that there is *an intercellular ground substance, either homogeneous or fibrillated, separating the specific cells of the tissue*.

Accepting this conception of the different characters of the different tissues, it will be seen that these may be divided into two great groups, which we may term, provisionally, the lining membrane group and the body pulp group. This division appears to me most important. While some pathologists, like O. Israel¹ and Buxton,² have already noticed this distinction, I do not know that histologists and embryologists have called adequate attention to it. Though I am strongly against the coinage of new scientific terms, there are occasions when this is absolutely necessary, and this appears to be pre-eminently one of these occasions. Thus I would term the lining membrane tissues *Lepidic*, from *λεπίς, λεπίδος*, a rind, skin, or membrane; and what I have termed the pulp tissue *Hylie*, from *ύλη*, crude or undifferentiated material or matter.³ We can go further and subdivide each of these main groups according as to whether the tissues are of

¹ *Berl. klin. Wchnschr.*, 1900, Bd. xxxvii. Ss. 609, 644, 667.

² *Journ. Cutan. and Genito-Urin. Dis.*, N.Y., February and April 1901.

³ I would here acknowledge my indebtedness to Principal Peterson, of McGill University, for aid in the selection of these terms.

epiblastic, hypoblastic, mesothelial, mesenchymatous, or endothelial origin. On this basis we obtain the following classification of normal tissues :—

I. LEPIDIC, OR LINING MEMBRANE TISSUES,

in which the blood vessels do not penetrate the groups of specific cells, and in which there is an absence of definite stroma between the individual cells, although such stroma, of mesenchymatous origin, may be present between the groups of cells.

1. EPIBLASTIC—

Epidermis. Epidermal appendages—hairs, nails, enamel of teeth, etc. Epidermal glands. Epithelium of the mouth—salivary glands. Epithelium and glands of—nasal tract and associated spaces. Epidermal portion of hypophysis cerebri. Lens of eye. Epithelium of—membranous labyrinth of ear, anus, male urethra (except prostatic portion).

2. HYPOBLASTIC—

Epithelium of—digestive tract and glands connected with it. Specific cells of—liver, pancreas, tonsils, thymus, thyroid. Epithelium of—trachea, lungs, bladder, female urethra, male urethra (prostatic portion).

3. MESOTHELIAL—

Lining cells of—pleuræ, pericardium, peritoneum. Specific cells of—suprarenals, kidneys, testes, ovaries (Graafian follicles). Epithelium and glands of—Fallopian tubes, uterus, vagina, vasa deferentia, vesiculæ seminales, etc.

4. ENDOTHELIAL—

Lining endothelium of—blood vessels, lymphatics.

II. HYLIC, OR PRIMITIVE PULP TISSUES.

Organs and tissues in which the special characteristic is that the specific cells lie in, and are separated by, a definite stroma, homogeneous, or fibrillar, in which there may or may not be blood and lymph vessels.

1. EPIBLASTIC—

Nerve cells, neuroglia.

2. HYPOBLASTIC—

(*Vide* note, p. 246).

3. MESENCHYMATOUS—

Fibrous connective tissues, cartilage, bone, reticulum of lymph glands, bone marrow, fat cells, involuntary muscle tissue, spleen, blood vessels, blood corpuscles.

4. MESOTHELIAL—

Striated muscle, including cardiac muscle.

With this conception of the two great groups of tissues, we can now proceed to classify the tumours, by which term I refer here to what Thoma has called "autonomous neoplasms." Of these there are two great orders, the Teratomata and the Blastomata. The former I have elsewhere defined as "tumours composed of the products of growth of one individual within the tissues of another individual of the same species," the latter as "tumours composed of the products of aberrant growth of cells and tissues of the individual in whom they are developed."¹ It is not necessary here to discuss the correctness of these definitions, for, however defined, I wish here to leave the Teratomata very largely out of consideration; they form a class by themselves, and whether we accept or do not accept the definition above given, we find that their mode of development and their characteristics follow—with complications—the lines about to be laid down with regard to the Blastomata. These latter form the more important class, and it is with them that I wish specially to deal.

Following this scheme of the classification of the normal tissues we may now divide these into two main genera—the *Lepidomata*, originating from the above lining membrane tissues; and the *Hylomata*, originating and derived from tissues developed from the embryonic pulp.

I. LEPIDOMATA, OR "RIND" TUMOURS.

A. Primary *Lepidomata*.

1. EPILEPIDOMATA.

Tumours whose characteristic constituents are overgrowths of tissues, derived directly from the epiblastic lining membranes, or true epiblast.

- (a) *Typical*.—Papilloma, epidermal adenomata (of sweat, salivary, sebaceous, and mammary glands, etc.).
- (b) *Atypical*.—Epithelioma proper, carcinoma of glands of epiblastic origin.

2. HYPOLEPIDOMATA.

- (a) *Typical*.—Adenoma and papilloma of digestive and respiratory tracts, thyroid, pancreas, liver, bladder, etc.
- (b) *Atypical*.—Carcinoma developing in the same organs and regions.

B. Secondary *Lepidomata*.

3. MESOLEPIDOMATA.

Tumours whose characteristic constituents are cells derived in direct descent from the persistent *mesothelium* of the embryo.

- (a) *Typical*.—Adenoma of kidney, testicle, ovary, urogenital ducts; adenoma of uterus and prostate; adenomas originating from the serous membranes, "mesothelioma" of pleuræ, peritoneum, etc.

¹ *Brit. Med. Journ.*, London, 1901, vol. i. p. 621.

- (b) *Atypical*.—Cancer of the above mentioned organs; squamous endothelioma, so-called, of serous surfaces, epithelioma of vagina.

4. ENDOTHELIAL LEPIDOMATA.

Tumours originating from the endothelium of the blood and lymph vessels; endothelioma, perithelioma.

II. HYLOMATA, OR "PULP" TUMOURS.

1. EPIHYLOMATA.

Tumours whose characteristic constituents are overgrowths of tissues, derived from the embryonic pulp of epiblastic origin.

- (a) *Typical*.—True neuroma, glioma.
(b) *Atypical*.—"Gliosarcoma."

2. HYPOHYLOMATA.

Tumours derived similarly from embryonic pulp of hypoblastic origin.

- (?) Chordoma.

3. MESOHYLOMATA.

A. **MESENCHYMAL HYLOMATA**.—Derived from tissues originating from the persistent mesoblastic pulp or mesenchyme.

- (a) *Typical*.—Fibroma, lipoma, chondroma, osteoma, myxoma, leiomyoma.

- (b) *Atypical*.—Sarcoma (derived from mesenchymatous tissues), with its various subdivisions, fibro-sarcoma, spindle-cell sarcoma, oat-shape cell sarcoma, chondro-sarcoma, osteo-sarcoma, myxo-sarcoma, melanotic sarcoma, etc.

B. **MESOTHELIAL HYLOMATA**.—Tumours which are overgrowths similarly of tissues derived from embryonic pulp of definitely mesothelial origin.

Rhabdomyoma.

It will be seen that in this classification I do not include the deciduoma malignum. As I have pointed out elsewhere,¹ accepting the view that the syncytium is of foetal origin and not maternal, these tumours have to be classed with the Teratomata, *i.e.* with the tumours originating in the growth of the cells of a second individual within the tissues of an individual of the same species.

If this classification be studied, it will be seen that we have done away with that deficiency in the earlier embryological classifications, whereby tumours of unlike orders and histological appearances were grouped together, and those of like characters separated. Gliomata, for example, come to be placed close to the mesenchymatous tissues, the gland-like tumours of mesoblastic origin become grouped along with those of epiblastic and hypoblastic origin.

Have we, in accomplishing this, introduced any new difficulties? One objection will undoubtedly present itself, namely, that among the Mesolepidomata we have grouped together tumours, some of which are of a strongly epithelial or glandular type, for example, the cancers of the uterus, with others, like the Endotheliomata, which tend to be

¹ *Loc. cit.*

distinctly of a sarcomatous type. But further consideration will show that this, instead of being a weakness, is a strong point in this classification. We have, that is, to recognise that among these Mesolepidomata, as above defined, we meet with several forms of tumours of transitional type—tumours which in their least aberrant portions show characters which approximate them to the Carcinomata, and in their more aberrant portions are undistinguishable from Sarcomata. And, indeed, it is only by a study of the embryogeny of the tissues from which these tumours are derived that we gain any satisfactory comprehension of the why and wherefore of these peculiar characters.

Here let me point out that, employing the terms here introduced, based as they are upon the embryogeny of the different tissues and the tumours derived from them, we may allow the terms "carcinoma" and "sarcoma," to revert to their earlier and purely histological significance. And I would emphasise, that it must not be understood that these terms, carcinoma and sarcoma, are to be regarded, and are by me regarded, as being synonymous with "atypical lepidoma" and "atypical hyloma" respectively. Rather, I would lay down that, accepting this nomenclature, we may safely speak of any tumour of the aberrant glandular type as carcinoma, whether it be of epiblastic or mesothelial origin, and any tumour of aberrant and so-called embryonic connective tissue type, as sarcoma, whether derived from the mesenchyme, the epiblast, *e.g.* glio-sarcoma, or even from the endothelium or mesothelium.

Of late years there has been an ineffectual attempt to restrict these two terms. Thus, many authorities have refused to speak of malignant adenomata of the kidney and suprarenal as being true carcinomata, and others have strenuously opposed the employment of the term gliosarcoma. Nevertheless, the same authorities, while refusing to speak of a cancer or carcinoma of the kidney, freely refer to carcinoma of the uterus, although, like the renal tubules and the suprarenal, the uterine mucosa is of mesothelial origin. In short, it has been proved impossible to employ these terms with embryogenetic limitations, and this introduction of a nomenclature, which is based upon embryogeny, ought, if accepted, to permit us to use them, as they ought to be used, in the purely histological sense.

It will be seen that I in no sense urge that (were it possible!) the use of these terms be done away with, for, accepting the purely histological use of the terms, we can unreservedly agree with Israel that it is a matter of taste whether we speak of a germ tumour as an "endothelioma carcinomatorum or sarcoma endotheliale." For routine clinical purposes they are most valuable. When a tumour has assumed a carcinomatous or a sarcomatous appearance it is coincidentally locally malignant, if not in all cases generally malignant also. The terms, therefore, have a clinical significance and value. Only, let me repeat, they are valueless for purposes of relationship and classification, and must bear no embryogenetic signification.

To explain these peculiarities of lepidomatous tumours let me point out that:—

1. After the embryonic period, it would seem that hylie tissues never take on lepidic characters. We have no instances, that is, in

which, after embryonic life, we recognise that lining membranes or glands become differentiated from connective tissues.

2. It is generally held that the converse is also true.¹ With regard to tumours we find the same principle evidently in operation.

3. We may confidently lay down that all tumours and portions of tumours, containing cell layers or cell groups of the lepidic type, have been derived from pre-existing lepidic tissue. Possibly this so-called principle is more of the nature of a postulate than of a proved law; we take it for granted, and may not be able to prove our position in every case. We have, that is, fairly numerous examples of neoplasms of lepidic type, developing in situations in which normal lepidic tissue is not present,—adenomatoid tumours of the bone, glandlike follicles in the midst of uterine fibroids, cysts, or tubular spaces lined by cubical or columnar epithelium in gliomata—and the list might be lengthened.

In by far the larger number of cases of this order, either the structure of the tumour so conforms to known neoplasms, the origin of which has been traced positively to some glandular organ, that we are convinced that the growth has originated from the inclusion of a portion of such glandular tissue, or we recognise that the growth occurs in some region, in which, during fetal life, there has existed some duct or portion of lepidic tissue, in a region, likewise, in which in the adult we occasionally encounter the persistent remains of the same. But pathologists, I believe without exception, agree to the sense of this postulate; we may not know, in all instances, what is the original tissue from which a heterotopic glandular tumour has had its origin, but we are absolutely sure that that original tissue giving rise to a glandular tumour has not been of the connective tissue type. We may therefore, I think, lay this down with confidence that tumours in which the cell arrangement is of the lepidic type, presenting columns or groups of cells, devoid of any stroma between the members of these columns or groups, have been developed from one or other lepidic tissue, and not from one of the hylic or pulp tissues.

4. We cannot, with equal confidence, make the converse statement, that tumours of the hylic type have always originated from hylic tissues and not from lepidic.

4a. I believe that I am right in stating that lepidic tumours of epiblastic and hypoblastic origin, however rapidly they grow, however

¹ True, that is, until Beard's rather startling observations upon the origin of leucocytes is confirmed. According to this observer the first, and indeed the main development of leucocytes is to be found as a process of proliferation and metamorphosis of the hypoblastic epithelium of the follicles of the foetal thymus gland. Beard's observations were published eighteen months ago, but to the best of my knowledge they still lack confirmation. Leo Loeb, also (*Arch. f. Entwicklungsrech. d. Organ.*, Leipzig, 1898, Bd. vi., and *Medicine*, April 1899), has thought to see connective tissue cells undergoing origin from the Malpighian layer of the skin: his observations have not gained acceptance. In lower forms of life, however, some definite cases of regeneration of hylic from lepidic tissues have of late been brought forward.

extensive and distant be their metastases, always, even in their most aberrant portions, retain lepidic properties. Wherever two or three of the specific cells of such a tumour are gathered together, they form alveoli with no stroma and no interstitial capillaries. To the best of my knowledge, no case is on record in which it has been satisfactorily proved that peripheral or metastatic growths of a typical carcinoma of epiblastic or hypoblastic origin have assumed definitely sarcomatous characters.

Possibly the careful studies now being made, in connection with the melanotic tumours originating in connection with the skin, may prove that this statement will need eventual revision. Authorities are still so much divided as to the exact origin of sundry tumours of sarcomatous type belonging to this group, that it is not possible to make an absolute statement concerning their origin. If, however, it can be proved that under certain conditions tumours originating from the Malpighian layer of the skin can in their growth lose their lepidic characters, *i.e.* can become possessed of a definite stroma passing between the individual cells, then we shall have to acknowledge that epiblastic *Lepidomata* can, in the course of their growth, revert to a more undifferentiated sarcomatous type.

In one very interesting tumour of the prostate, examined by me some years ago, I was for a time of opinion that I could recognise such a transition. Sections taken from the prostate itself showed beautifully the existence of a very typical carcinoma almost scirrhus in appearance; passing towards the bladder the type became that of carcinoma simplex. The abundant, apparently rapid, growth, forming a projection into the bladder itself, was so wholly cellular as to resemble a round-cell sarcoma, but more careful examination showed that even here the cells were arranged in alveoli, although the stroma between the individual groups was so delicate as to be traced with considerable difficulty.

4b. With mesothelial and endothelial *lepidomata* the same is not always so; the older or earlier portions of the tumour may show distinct adenomatoid or carcinomatoid characters—occasionally the whole tumour is typically adenomatous; but more rapidly growing portions are peculiarly liable to depart so far from type, so peculiarly liable to take on the appearance of embryonic connective tissue, that it becomes impossible, basing our terminology upon histological appearances, to say whether we are dealing with a carcinoma, or a sarcoma, or a mixed growth—a carcinoma sarcomatodes, or a sarcoma carcinomatodes. More particularly the increased recognition of the frequency of endotheliomata and peritheliomata has forced us to see the difficulties in our present mode of classification. The perithelioma when developing characteristically, apparently as an endothelioma of the perivascular lymphatics, may strongly resemble an adenoma in the regular columnar arrangement of its cells, and yet other parts of the same tumour may be absolutely sarcomatous in type. And while the ordinary endothelium, such as one so commonly meets with forming tumours in connection with the membranes of the brain, is in general characteristically sarcomatous in structure, areas are to be detected here and there, indicating its origin as a squamous proliferation of the

lymphatic or blood vascular endothelium. Without, I trust, taking anything from the interest and value of his forthcoming article upon this subject, I would here note that Dr. P. G. Woolley, Fellow in Pathology at McGill University, has just completed a most elaborate and minute study of a tumour, originating in the zona fascicularis of the suprarenal, in which a similar transition from adenomatoid to purely sarcomatous structure is to be followed without the possibility of doubt.

Here, then, are tumours which, showing in the least aberrant regions indications of origin from a lining membrane or lepidic tissue, are apt to take on the appearance and structures more characteristic of "pulp" tumours.

Now this difference in behaviour between the Epilepidomata and Hypolepidomata on the one hand, and sundry of the Mesotheliomata and Endotheliomata (Mesolepidomata) on the other, is but consonant with embryological observations and the broadest biological principles. One great principle which we see constantly in evidence, is that those structures and properties which are of oldest acquirement are those which are last to be lost; it is the most recent acquirement which tends to be the earliest to disappear. We see this exemplified continually in connection with the Blastomata. The more rapid the growth—the more the cells of a tumour depart from their normal mature environment—the more do we observe that those features of the tumour cells, which are specific for one or other tissue, tend to disappear. In the most rapidly growing and most aberrant tumours the individual cells afford us little or no clue to the tissue of origin. It is the general arrangement of the cells that aids us in making our diagnosis, and even the general arrangement is not so much that peculiar to the fully grown tissue, as that common to connective tissues in general, or to glandular or lepidic tissues in general. We recognise a reversion to an earlier, simpler, or, as we express it, embryonic type. As I have pointed out elsewhere a distinction must be recognised between the functional and the proliferative, or vegetative, activities of cells; the essential feature of the cell of the atypical tumour is the replacement of functional by vegetative activity, and the consequent loss of those features which are directly associated with the performance of function.

I would now suggest that we carry the working of this principle a little farther back. The first lining membranes to be differentiated are the epiblast and hypoblast; their differentiation, indeed, is one of the earliest events in developmental history; and this being the case, we should expect—and we find—that tissues, whether normal or neoplastic, derived in direct line from these two layers, are singularly tenacious of their properties as lining membranes, and so it is that Epilepidomata and Hypolepidomata always show evidences of their lepidic nature. We should not expect—and we do not find—that

where this direct line has been departed from, where, for example, hypoblast has given off masses of cells to form mesoblast, and the epiblast similar masses to form the neuroblast, that, in reversion, tissues derived from mesoblast and neuroblast respectively should again enter upon the lining membrane stage. Where in the process of development an organ or part is formed by the cells of tissue of a higher order assuming a less differentiated condition, and from this lower state proceeding to develop along special lines, we do not find that in reversion and degeneration that tissue passes beyond the less differentiated stage, and then proceeds to show characters of a primary more differentiated condition. Thus it is that the mesenchymatous tumours and sarcomata in general show no tendency to assume lining membrane or lepidic characters, even though, without exception, all these tissues have primarily arisen as derivatives from either epiblastic or hypoblastic lining membrane.

If occasionally in gliomata we find cysts lined with columnar epithelium, this is not an example of such reversion to the more primitive epiblastic characters of the glial tissue. Those who have studied cases of this order have, without exception, ascribed such conditions to inclusions of rests of embryonic tissue containing portions of the *Anlage* of the central nervous canal.

But now, coming to the mesoblast, we know that it is at a later date in the history of the embryo that this becomes differentiated into mesothelium and mesenchyme, and the development of the mesothelium is in the direction of increased specialisation. Thus we should expect—and we find—that in processes of a reversionary type these more lately acquired characters are more capable of being lost, so that growths formed from organs of mesothelial origin are more liable to pass back, and to assume characters approaching those of the primitive mesenchyme and mesoblast, than are growths from hypoblastic and epiblastic organs to revert to what we might term the morula stage. And if it be correct to regard the endothelium as a still later development from the mesenchyme, then we can understand how it is that Endotheliomata are peculiarly liable to take on the characters of the primitive pulp tissue from which endothelium became differentiated.

Israel¹ recognises fully this same dependence of the characters of the endotheliomata upon the embryogena of the mother tissues, for he remarks (the italics are mine):—“Diese (endotheliale) Deckzellen *haben sich nicht unter allen Umständen in ihren Eigenschaften von diejenigen ihrer, Intercellularmasse bildenden, Stammesgenossen so weit entfernt*, dass nicht auch sie gelegentlich wieder befähigt würden, Intercellularmasse hervorzubringen, deren Qualität von den ererbten Eigenthümlichkeiten abhängig ist. . . . Gelegentliche Vorkommnisse in den Endothelgeschwülsten und auch bei gewissen entzündlichen Neubildungen zeigen, dass die Fähigkeit Intercellularsubstanzen zu produciren, manchen in Tumoren gewachsenen Endotheldescendenten, *nicht unwiederbringlich verloren gegangen ist*, wie den Epithelien.

¹ *Loc cit.*, p. 668.

Das ist aber auch der für die Diagnose praktische bedeutsamste Unterschied endothelialer Krebse gegenüber den epithelialen, und er macht von allen die Uebergangsformen vom Endotheliom zum Sarkom verständlich."

I am far from saying that this is the one and sufficing cause why certain orders of the Mesolepidomata have this marked tendency to assume more sarcomatous characters. I do not think that this is everything; nevertheless it does, I think, materially aid us to understand why this peculiarity in the progressive development of these tumours manifests itself: it is one factor. Indeed, it is not all the Mesolepidomata which present these same tendencies. To give one example: we never, to my knowledge, find that carcinomata of the uterus, either in their more rapidly growing parts or in their metastases, show other than well-developed cancerous structure. In fact, there is singularly little distinction to be drawn between the characters of cancers originating from the uterine mucosa and those of epiblastic and hypoblastic origin. The same is true with regard to the tumours of the Fallopian tube. And, so far as I see, we have to lay down also that the high grade of specialisation and differentiation of the lining cells of a membrane is accompanied, *pari passu*, by a lack of capacity to undergo reversion to the simplest type. While, for example, the glial cells are apt to undergo rapid proliferation and form tumours of a simple cellular type, true Neuromata are extraordinarily rare, and in general we may lay down that the high degree of differentiation which has been reached by the neurone has taken from it, to a very large extent, the power of proliferation. This is, it is true, an extreme example. The cells of the uterine mucosa are not nearly so highly differentiated; they are, however, distinctly more specialised than are endothelia, and the cells lining the serous cavities. And, I would add, more differentiated than, for example, the cells of the cortex of the suprarenal, which but attain an arrangement in solid columns resembling that seen during the process of development of certain other glandular organs.

Thus it may be that simplicity of type is one factor determining why certain tumours revert from a more carcinomatous to a more sarcomatous type. I mention this as a possible factor, and would not dwell too strongly upon it; rather I would admit, and that willingly, that here we are in the region of analogy and hypothesis. Just as we are unable to explain why in one case, in a given organ, we have produced, for example, a relatively benign adenoma; in another, in that same organ, an actively growing and malignant carcinoma; so it may be that full consideration will show that here also we have to recognise, without possibility of explanation, that, in connection with tumours of one organ, the lepidic properties are retained with remarkable persistence, while in tumours of another organ, derived from the same cell layer, these same properties are lost with comparative ease. But it seems to me not without its use, to point out tentatively a

possible factor in the development of the different properties of different tumours. As a group it has to be admitted that mesothelial and endothelial tumours exhibit this tendency to assume a more sarcomatous appearance.

We are thus justified in separating *Lepidomata* into two main divisions,—the *primary lepidomata*, wherein we include the tumours derived from tissues of direct descent from the epiblast and hypoblast, and the *secondary or transitional lepidomata*, which include tissues of indirect descent from the same, and which may as a consequence show what I may term transitional characters. Making this division, I leave it open as to whether we speak of the tumours of the first order only as the true *carcinomata*, and refer to those of the second order as at most *carcinomatoid*, or speak of all tumours of what I may now without confusion refer to as having lepidic characters, as being *Carcinomata*. My preference, as I have already stated, is for employing this term purely in a histological sense.

Recognising that many years have passed since I was engaged in the active study of embryology, I have not ventured to publish this paper without consulting those most capable of pronouncing authoritatively upon the embryological problems here involved; and I would here express my sincere thanks and sense of deep obligation to Professor Charles Sedgwick Minot of Harvard, and Professor Carl Huber of Ann Arbor, for their most kind criticism and suggestions in connection with the views here elaborated. I very gladly acknowledge also that I owe more particularly to a correspondence with Professor Huber, now some months ago, my recognition of the importance, from a pathological point of view, of distinguishing between the mesothelial and mesenchymatous derivatives of the mesoblast.