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On Growth and Overgrowth and on the
Relationship between Cell Differen-
tiation and Proliferative Capacity;
its Bearing upon the Regeneration
of Tissues and the Development of
Tumours.

BY

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TIATION AND PROLIFERATIVE CAPACITY;
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THERE are in medicine and other sciences not a few beliefs and ideas which we have taken up we know not how, and which in general we no more think of discussing than we do, for example, the subject of good manners. Thus, just as it is difficult if not impossible for us to state how or where we gained any single article of our code of personal ethics, so it is with certain of these general ideas in medicine; and while we have never discussed these beliefs we feel individually assured that they are the current ideas of other workers along the same lines.

One of these tacit beliefs or comprehensions relates to the subject of the growth of tissues. Asked off-hand we should assuredly, each one of us, state as his familiar belief that muscle arises from muscle, epithelium from epithelium, nerve cell from nerve cell, and so on, and the mental picture which we form of the process of growth is, I fancy (though here, of course I speak under correction), that the fully formed epithelial cell undergoes mitosis and divides into two, and so with the cells of

* By the courtesy of the Editors of the "Festschrift," to be published in honour of the seventieth birthday of Dr. A. JACOBI, of New York, we are enabled to publish this article coincidentally, to all purposes, with its appearance in the volume in question.

other tissues. Yet if we think a little longer and recall what we have actually seen under the microscope, this mental picture is seen to be incorrect or, at least, imperfect. Thinking recently over this matter it has been impressed upon me that if we obtain a correct idea of what occurs during the process of growth of tissues, we not only realize that there is a very broad biological law underlying this process of growth from the earliest stages of the embryo upwards, but further, applying this biological law to the subject of pathology, we gain a deeper and a fuller comprehension of certain matters bearing upon regeneration and degeneration of tissues, and what is more, bearing very directly upon certain of the phenomena of tumour growth.

While the individual, formed as he is of a marvellous complex of various tissues, is a reproduction of the tissues and organs present in his paternal and maternal ancestors, he is the outcome and development, not of the combined fully developed tissues, nor again of any one highly differentiated cell or cell compound, but of a single undifferentiated cell—the fertilized ovum—a cell neither of the component parts of which, ovum or spermatozoon, has ever through the whole course of the ages been derived from other than similar undifferentiated cells; or, in other words, these apparently simple germ cells are capable of giving rise to the whole series of cells forming the whole mass of tissues from the simplest connective up to the most highly differentiated nerve tissue.* If we study the process of the development of the embryo, whether in plant or animal life, we see again a somewhat similar phenomenon.

From a very early period in such growth we recognize that certain cells alone appear to be actively dividing and to be actively proliferative, whereas other cells, the products of these, while they take on characteristic appearances, do not thus divide. Very early indeed in the developing embryo we recognize this existence of what may be termed "mother-cells,"—cells which themselves

* It is possible that while the cell body of these germ cells is relatively undifferentiated, the nucleus is peculiarly highly elaborated. We have, indeed, not a few indications that this is the case. Thus it may be that nuclear and cytoplasmic differentiation, in germ, and 'mother'-cells and in specific tissue, and 'daughter'-cells respectively, are in inverse ratio. We have not as yet reached a point at which any definite statement can be made in this connection. (Throughout this article I refer to cytoplasmic and not nuclear differentiation.) (Quoted by Barfurth zur Regeneration der Gewebe, *Arch. f. Mikrosk. Anat.* 37, 1891, p. 424)

End of note p. 8.

remaining embryonic in type give rise by division to other cells which assume more highly differentiated characters. And this is true not only of animal organisms, but still more obviously of plants: we have but, with Sachs, to study the growing points of plants to realize the existence of these "mother-cells."

Now when we pass to the fully formed individual, we must still recognize this fact, which we are apt to pass over, namely, that the specific cells, if I may so term them, of the different tissues—that is, the highly differentiated and characteristic cells of those tissues—do not themselves give rise directly, and by division, to other specific cells, but that in each tissue there are these more or less undifferentiated mother-cells, which more especially have the power of proliferating, and it is the daughter-cells which assume the full specific properties in the different tissues, or if, as would seem to be the case in some instances, the active cells of certain not very highly differentiated tissues themselves proliferate, they only do this *after a preliminary reversion* to a "mother-cell," or more embryonic type.

Let me here give a few examples: Immediately I mention them, everyone will realize that these are facts thoroughly familiar. One of the simplest cases is that of the skin: in this it is the lowest layer of the epidermis, the Malpighian layer, whose cells undergo active proliferation, and this constantly, throughout the whole period of life, and the cells which are most active in the process are those of the very lowest layer—cells which are of a permanently embryonic type.

After injury, it is true, we may come across occasional mitotic increase, more especially in the lower animals, in the region of the prickly cells, but, when we do, we see that it is accompanied by reversion of the cell to a simpler type: the prickles or bridges disappear, the cell loses its connection with the neighbouring cells, and passes back to a simpler stage prior to multiplication.

In bone the case is the same. Production of bone tissue is *not* brought about by multiplication of the pre-existing and characteristic bone cells, but by osteoblastic tissue; or, in other words, by the mother-cells of bone lying in the immediate neighbourhood of the vessels of the inner layer of the periosteum, or again coursing through the Haversian canals and between the

laminae. When through injury or otherwise a stimulation is afforded, it is these mother-cells which applying themselves to the pre-existing bone multiply, and there governing the spaces around them lead to the deposit of a calcareous or bony matrix and gradually assume all the characters of typical bone corpuscles.

From the variability of the structure of the glandular organs it is difficult to lay down any general rule with regard to regeneration of glandular epithelium, so that it must be confessed that, partly on account of this variability, partly on account of the fact that the different observers upon glandular regeneration have not had this conception of mother-cells before them in their studies, such glandular epithelium in the present state of our knowledge affords the least satisfactory demonstration of the principle. There are, however, so many instances concerning which we have positive information, as to render it more than probable that throughout the same principle is in action.

Of the mother-cells of the type seen in the Malpighian layer of the epidermis, several instances may be called to mind: the mother-cells of the testicular epithelium and (though differing somewhat in plan) of the ovarian follicles, of the sebaceous and, apparently, from Tornier's studies, the mammary glands. In both of the latter organs there is, during activity, a giving off of cells, and mitosis occurs especially in the deeper, more external layers.

In this connection should, I think, be mentioned the columnar and ciliated epithelia of mucous membranes. It is remarkable how one histological text book after another figures such columnar epithelium as formed of a palisade of fully developed columnar cells in regular series situated upon the basement membrane, without indicating or even referring to the presence of embryonal "mother-cells" lying between the bases of the fully differentiated columnar cells. Certainly under pathological conditions one is impressed by the fact that these basal cells are present, and that there is a development of new cells from beneath to take the place of the degenerating fully formed cells. While in the simpler acinous glands it is difficult to recognize such permanent mother-cells (indeed they are probably absent in the adult), here at least they are present.

In the lymph glands we may have another arrangement. In them the mother-cells are collected together in the form of small nodes in the centres of the individual follicles: a somewhat similar arrangement of foci of embryonal cells is met with in the thyroid, while in the pancreas, Langerhans's bodies or "cell accumulations" would seem to be of a similar nature, although this is not as yet absolutely determined. /w

Closely allied to this condition is what is seen in the lung and again in the serous coat of the peritoneum (though neither of these, it is true, comes strictly under the category of true gland structure). In the former, certain more embryonic cells persist, especially at the angles of junction of the alveoli, and these are generally regarded as centres for the normal proliferation and regeneration of the alveolar epithelium. On the peritoneal surface also there are found clumps of smaller cells capable of active proliferation. With regard to both these cell layers, the flattened—differentiated—cells are liable, under irritation, to revert to the fuller, more rounded embryonic condition and then undergo mitosis and proliferation.

Judging from the fact that mitoses are not observed in the fundal portions of several acinous glands, while they are frequent in the neck regions of the same, it would seem at least probable that mother-cells, or cells capable of reverting to the mother-cell type, are situated in the latter area. But generally in acinous glands of simple type there is, as Bizzozero has pointed out, little evidence of continued proliferation under normal conditions, once they are fully formed. In connection with these, it is that more exact studies are requisite; certainly in some, *e.g.*, in the kidney tubules, slight continued irritation leads to the differentiated cells, undergoing proliferation, but at the same time these cells are seen to revert to the simpler more embryonic type. Thus, while confessing that it is not as yet possible to demonstrate in every case that neither mother-cells are present or that for regeneration the differentiated cells revert to a more embryonic type, the number of examples that can be brought forward, where either one or other of these processes is seen to occur, is so large that we may assume that a general principle obtains in connection with all.

Passing now to another tissue, namely muscle, the process of regeneration, as pointed out by Barfurth, varies largely.

In connection with the muscle, the process of regeneration, as pointed out by Barfurth, varies largely according to the age of the individual. Originally the muscle fibres, it is needless to say, are recognised as arising from a series of cells known as *sarcomblasts*, relatively large cells with abundant protoplasm, the nuclei of which tend to proliferate, and along one aspect of, or generally around, the periphery there is gradually developed first a longitudinal fibrillation, and then transverse striation. In young larval forms of amphibia, for example, after injury such *sarcomblasts* may be seen to be present, to undergo multiplication, and to give rise to typical muscle fibres; here, therefore, very clearly there are mother-cells. The existence of such in the adult is still a matter of dispute; for in the older individuals two processes have more especially been recognized: one, that in which the fully formed muscle fibres become the seat of an active nuclear proliferation, and then in certain areas of the fibres the striation, more especially toward the end, or laterally, becomes indistinct and little buds containing nuclei are given off, which become the precursors of the new growth. Or secondly, as pointed out first by Weismann, there may be recognized, even in perfectly normal muscle of adult animals, certain occasional spindle-like bodies, consisting of short striated muscle fibres, characterized by very abundant nuclei and, according to Kölliker and others, these bodies represent centres from which by longitudinal division new fibres are given off. Even in this case it will be seen that these bodies represent a lower imperfect stage of differentiation, and the richly nucleated mass may strictly be regarded as a "mother-cell."

Thus from a study of the process of regeneration as seen in the different tissues in man and vertebrates generally, it is possible to lay down the following laws:

1. The fully differentiated cells of a tissue proper never arise from cells that are themselves fully differentiated.
2. Under the *normal* conditions of growth and during physiological regeneration, the fully differentiated cells would seem in nearly every case to be developed from "mother-cells"—undifferentiated or but

partially differentiated cells which themselves throughout the term of life of the individual never attain to the full differentiation peculiar to the tissue to which they belong and which indeed they produce. For these mother-cells by division give origin to the daughter-cells, and it is the daughter-cells which attain full differentiation and form the specific cells of the tissue. More rarely the functional cells themselves, by reversion to a more embryonal type, can take on the properties of mother-cells.

3. Under *abnormal* conditions, the fully differentiated functioning cells of certain tissues are capable of proliferation and giving rise to cells of like nature, but this is only after a preliminary reversion to a simpler, more embryonic type. The fully differentiated cell as such is incapable of proliferation.

4. Or, otherwise, the energy stored up by the cell may be expended in one of two directions, but not in both—either in functional activity or in preparation for proliferation, and, the structure of a cell being the expression of the activity of that cell, the expenditure of energy in either direction is attended by corresponding morphological or structural differences in the cell.

5. The more highly differentiated a cell, the more highly elaborated its structure, the less the ease with which it reverts, and the less the liability to reversion to a simpler reproductive form; the simpler the cell, the greater the ease and the greater the liability to such reversion. It is thus possible, at the one extreme, to conceive cells so simple in function and in structure that functional or reproductive activity may be called into play indifferently without *recognisable* preliminary structural alteration, and, at the other, cells so highly differentiated that the capacity for proliferation has become entirely lost.

The law with its corollaries here given does not so far appear to have obtained general recognition. Certainly I fail to find it explicitly referred to by writers upon morbid anatomy, and had it been currently accepted by biologists it would ere this have become part and parcel of pathological teaching. It is only after some little search and almost by chance that I find its main paragraph laid down by Kölliker in 1885, and that only, as it were, in passing, in an article not dealing directly with regeneration, but dealing with the part played by the nucleus in inheritance. In that article Kölliker states: "In all cases in which an organ or a tissue is capable of regenerating itself, it

must contain elements of an embryonal character, or at least such elements as can take on that character." And again, in the same article: "These cells then are dependent upon the same law, as, in the embryo, is the formation of organs."*

But in the general portion of his great *Handbuch der Gewebelehre des Menschen*, published in 1889, I cannot find that he again refers to this principle, hence it would appear that he did not realize its wide application.

Thus, although the law when once grasped is simple, almost to the verge of being a truism, it merits being stated for once in as clear terms as possible that its high importance may be fully recognized.

Applying now these considerations to certain pathological conditions, it is in the first place necessary to say but little concerning pathological regeneration and repair, for I have already applied some of the facts gained from a study of such regeneration in the development of my argument. Thus much, however, may be said, that the more we study the regeneration of various tissues, the more we see that the phenomena of the process fall into place in consonance with the law above laid down. The cells of a regenerated tissue are derived from the pre-existing cells (and mother-cells) of that particular tissue, and the more highly differentiated the tissue the less is its capacity for regeneration.

Of all cells, those which are the most highly differentiated, namely the nerve cells, show the least capacity for proliferative regeneration; there is a remarkable lack of evidence of fully developed nerve cells having been observed in the process of mitosis, and, corresponding with this lack, when we consider the histological basis of motor, sensory, and mental acts, it is *a priori* hard, if not impossible, to conceive a given cell in any of the higher nerve centres undergoing proliferation without there being simultaneous arrest, not to say loss, of function. Every-

*Kölliker: "In allen Fällen, in denen ein Organ oder ein Gewebe fähig ist sich wieder zu erzeugen, muss dasselbe Element von embryonalem Charakter enthalten oder wenigstens solche, die diesen Charakter anzunehmen im Stande sind." "Diese Zellen bedingen dann nach denselben Gesetzen, wie beim Embryo, die Organgestaltung." — "Die Bedeutung der Zellenkerne für die Vorgänge der Vererbung," *Zeitschrift f. wiss. Zool.*, Vol. xlii., 1885.

thing indicates that of all the cells of the body the neurones are those endowed with the longest life period.

During foetal or larval life, prior to the attaining of full function, such proliferation has been recognized (Barfurth), or otherwise, the incompletely differentiated nerve cells may take part in the regenerative process; though it may be considered an open question whether the new development of neurones in experiments upon the spinal cord of the larval newt and other amphibia is the result of proliferation of developed neurones or of mother-cells.

That such mother-cells must exist even in the human nervous system has been forcibly brought home to me by a study of certain sections of the spinal cord to which Dr. Shirres, working in my laboratory at the Royal Victoria Hospital, recently called my attention.

These sections are from a case of porencephalus in which apparently, from all indications, the atrophy and disappearance of practically the whole motor area in the left hemisphere dated from the last month or two of foetal life. Despite this practically complete loss of the entire motor area on the left side, the resulting evidence, of paralysis and disturbance of function were little more than a relatively slight want of development of the bones and muscles of the right side of the body together with paresis of the musculature of the right hand. In the cord the difference between the two motor tracts is most marked, there is entire absence of the crossed pyramidal tract on the left side, of the direct pyramidal on the right, and, corresponding with this, there is a most marked atrophy of those groups of cells towards the periphery of the anterior horn of the grey matter on the right side which everything indicates as being connected with the crossed pyramidal tract and being what I may term the spinal motor centres for the upper extremity. But in sections in which this atrophy is most marked there is a distinct increase in the number of ganglion cells in the deeper and more central areas of the grey matter; here the number of cells is much above the normal, the cells are large and more numerous than those of the left side in the same section.

For our present purposes it is clear that these abundant cells

cannot be regarded as due to proliferation of the atrophied cells—their relative position forbids such an assumption. Their existence, however, is strongly in favour of the view that they have been derived from mother-cells in the grey substance.

The regeneration of nerve fibres is another matter. So far as regards the axones, or axis-cylinder processes themselves, it is strictly comparable with the new growth of the cell substance of the amoeba when a part of that cell substance has been removed without direct injury to the nucleus. As regards the investing sheath of the medullated nerve fibre, regeneration here is in strict accordance with the third law, there is a preliminary period of reversion; the formed substance (myelin), governed or elaborated by the cell, breaks down, the nucleus becomes more prominent and surrounded by an increased amount of protoplasm, and then in place of a single nucleus of a node of Ranvier one gets numerous nuclei, and the new cells evidently surround the newly developed axis cylinder as it grows downwards from the seat of injury.

I have already referred to the regeneration of muscle, but if now we pass to the other extreme and consider what happens in the simplest of all tissues namely, white fibrous connective tissue, we find that even here for pathological regeneration to occur there is a preliminary stage of swelling of the connective-tissue cells, the nuclei become larger and more prominent, the surrounding protoplasm becomes increased in amount, the surrounding fibrils tend to disappear, and now, only after this reversion to a simpler, more embryonic condition, do we have proliferation and the subsequent building up of new connective tissue.

To enter here into a discussion as to whether connective tissue can be formed from wandering cells and whether any special form of wandering cell is capable of taking part in such new formation, would be imperative if I were dealing more especially with the law that tissues arise from pre-existing specific tissue cells; here rather, dealing with the process and the law of growth, with the law of mother-cells, if I may so term it, the very limits to which this article is confined by the editors must be an excuse for not dealing with this subject.

A few words, however, must be said with regard to metaplasia in general, for the law of reversion to a more embryonic type is distinctly in evidence throughout, and indeed helps us to understand how, for example, a columnar-celled epithelium can be converted into a squamous-celled epithelium and one form of connective tissue into another; or, otherwise, metaplasia is never direct, but is only brought about by preliminary reversion to a more embryonic type, or, where mother-cells are present, by the modified development of cells derived from the mother-cells, the influence of environment altering the character of those daughter-cells during the period of growth.

If the principle be correct that the more highly differentiated a cell, the less its capacity for proliferation; or, in other words, the more the daughter-cells depart from the type of the mother-cells, the less their proliferative capacity, then the converse would seem to hold—that *the more the daughter-cells in a given tissue retain the characteristics of the mother-cells, the greater their proliferative capacity.* Or—to continue the argument—if through any cause the daughter-cells in a tissue do not attain full specific differentiation, then they are peculiarly liable to proliferate and function, not as specific cells, but as mother-cells. And further, as Bizzozero has pointed out, tissues in which the cellular elements exhibit frequent mitosis are those which more especially are liable to be the seat of excessive growth and tumour formation.

I am far from saying that this is the one principal concerned in the development of the blastomata or tumours proper, but I would urge that it is one important principle. It is outside the limits of this article to consider what is the essential stimulus or what are the stimuli leading to neoplastic growth; accepting, however, for the moment, that, whether temporarily or permanently, some stimulus or stimuli be in action, at least we gain a comprehension of why in the first place histioid tumours (in which one or other tissue is more or less faithfully reproduced) are essentially benign; and in the second place why malignancy and excessive cell proliferation, which is the essence of malignancy, go hand-in-hand with tumour formation of a pronounced embryonic type.

The failure to recognise the normal existence of mother-cells

in those tissues which are prone to tumour formation is very obvious in reading over Cohnheim's chapter upon tumours and in following the course of the argument which led him to conclude that tumours arise from latent superfluous embryonal tissue lying either within a tissue of the same nature or heterotopic.

While we must admit the existence of such embryonal rests in order to explain the development of such tumours as, for example, myomata of the kidney and primary cancerous growths developing in bone, the permanent existence of these mother-cells as the normal constituent of the tissues throughout life is wholly adequate to explain most benign and malignant tumours. To this larger conception of what is "embryonal tissue" we must, I think inevitably come, and with Senn and others we must regard tumours as product of tissue proliferation of embryonic cells of either congenital or of post-natal origin, even though we at present continue unable to state definitely what it is that immediately induces these cells to undertake excessive growth. Granting this, that in tumours we have aberrant tissue growth and that that tissue growth is due to certain cells assuming excessive proliferative properties wholly outside the needs of the economy, then such proliferating cells are to be considered as being derived :

1. From embryonic cell "rests" which have for a shorter or longer period remained latent in one or other tissue and then have taken upon themselves a rapid proliferation leading to tumour formation.

2. From the mother-cells of a tissue which, remaining undifferentiated, but capable of active proliferation throughout life, now assume excessive proliferative powers, their daughter-cells retaining to a greater or less extent the characters and the properties of the mother-cells.

3. From differentiated cells which reverting to a simpler, more embryonic type, with this reversion gain the capacity for active and excessive proliferation.

Possibly, I may add that the tendency to the development of glandular cancer in later life bears some relationship to the reversion and degeneration of gland cells at this period. As the tissues become exhausted, the more highly differentiated cells tend to become structurally simpler, revert, that is to say, to a

simpler type, and with this simplification of structure accompany atrophy there may be, I would suggest, along the lines already laid down, a greater liability for those cells to assume proliferative powers.