THE TRANSMUTATION OF THE EPITHELIUM OF THE TONSIL INTO CONNECTIVE TISSUE CELLS.

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I take the opportunity of the interest which the recent observations of the experimental work on cancer in mice have excited in the actuality of the conversion of an epithelial growth into a connective tissue growth, often surmised in clinical experience, to advance more expressly some observations of my own which long ago undermined my belief in the integrity of the theory of the separate destiny of the blastodermic layers. In a more extended discussion¹ of the question of this mutability as it presents itself in the study of the various forms of cancer, I have alluded incidentally to the appearances presented by the basal layer of the epithelium in various chronic inflammations of the mucosa of the nose and throat, especially that presented by the epithelial layers covering the various forms of lymphoid hypertrophy. I have alluded to the basal-celled epitheliomata, in the classification of Krompecher, as furnishing evidence of a transition of type between a malignant hyperplasia of epithelium and a malignant hyperplasia of connective tissue; but in the tonsil we find, it seems to me, a still more convincing evidence of this mutability, a belief which some histologists look upon as the rankest heresy and the most revolutionary of tendencies in the study of normal and pathological anatomy. Now the intelligent study of pathological anatomy must be based on the knowledge of normal anatomy which we possess, but indisputable as this may be if we leave out of account the dynamic agencies of the pathological state in their influence on structure, and still more, if we are ignorant of all that has been revealed in general biology in the last few years, we are liable to go farther astray than if we are occasionally forgetful of the overworked embryological dogmas of a former generation. Just as a new environment throws a plant into a state of disturbed equilibrium which results in a wider sweep of the curves of variation, and may even result in a true mutation in the definition of De Vries, so a state of chronic inflammation such as we so commonly meet in the pharynx of adolescence furnishes a stimulus to variations in the morphology of the surface or glandular epithelium. The epithelial cells under this irritation exude horny

1. New York Medical Journal.

scale-like masses at the surface, which are often called pachydermia, after the animals which have owed their characteristics to the same variations and mutations in their phylogeny. The keratosis and the pachydermia of the pharynx and larynx have inadvertently acquired a nomenclature all the more significant biologically because laryngology has been innocent of participation in any biological strife as to evolutionary theory. So when we come to look for variations and mutations beneath instead of on top of the epithelial line, what do we find?

I avail myself of a quotation from an article of Cordes² written many years ago when he had little support from histological or biological theory and observation:—"The finer construction of these gland-like inversions of the mucosae of the pharynx [analogous to the tonsillar crypts—J. W.] in advanced instances is as follows: The external cell covering (i. e., those cells lining the cavity) consists of one or two or more layers of markedly flattened and partly detached pavement cells; then comes a zone which is composed of still plainly connected groups of epithelial cells, mixed with ovoid epitheloid elements. The latter cells have a smaller amount of protoplasm (cytoplasm) than the epithelial cells and a round bladder-shaped nucleus which resembles that of the epithelium but is somewhat smaller. In this zone one finds in the epithelial cells as in the other elements separate karyokinetic division figures; many epithelial cells or groups of the same send between the round elements long protoplasmic prolongations which are again connected with other similar cells; many isolated epithelial cells are long stretched out, the nucleus is flattened, and one recognizes protoplasmic prolongations running in various directions. Further towards the periphery the cells so situated often appear somewhat smaller and more of an oval shape; the nuclei are more easily stained, more rich in chromatin. Finally there follows in many places a zone which is composed of small typical lymphatic elements. We have to do here in no way with a simple process of lymphoid element penetration through the epithelium."

I have translated this long excerpt from Cordes in order to give him full credit for having arrived long ago at a conviction,—or near it at least, for I have not again read his article in full,—which I also have for some time entertained—viz., the conversion of epithelium into connective tissue elements under certain conditions of

2. *Archiv. fur Laryngologie*. Bd. XII, 1902.—I am reminded of this valuable work of Cordes by a more recent article of Levinstein (*Ibid.*, Bd. XXI, hft. 2, 1909).

the mucosa of the nose or throat, in despite of the early teaching of my youth. How often this occurs I am not prepared to say. I have observed it most frequently in acute exacerbations of chronic inflammation of the tonsil. I have never seen a satisfactory indication of it without the presence of the hyperplasia of chronic inflammation. Over long stretches of the surface of the tonsil the genetic connection cannot be convincingly traced, but the observer will not infrequently arrive at fields under the microscope where the evidence is overwhelming and, to the unbiased mind, conclusive. Cordes, according to Levinstein, not only believes that the large lymphocytes are derived from the epithelium through gradations of so-called epitheloid cells, but that they form centers from which the smaller leucocytes are derived. Thus the epithelial layers furnish an endogenic center for the manufacture of a lymph node. This is also the view of Retterer, but it was radically opposed by Stohr.

I am prepared to accept the view that the lymphocytes are often derived from the epithelial cells and are subsequently transformed into fibroblasts and thus manufacture or help to manufacture the fibrous planes of the hyperplastic tonsil, but I have no reason to believe that this is the sole origin of the large lymphocytes of the tonsil. I cannot from my own observation say that in the tonsil the lymphocyte is the origin of the leucocyte, whether the former is derived from the epithelium or not, yet I believe that such is the case, since in other situations (bone marrow, the liver, etc.) it has been amply described by many independent observers. No one who has worked at the histology of the tonsil can fail on the other hand to confirm the statement of Stohr that the lymphocytes often penetrate the epithelial layers and lie in the crypt in great numbers. So far as my observations go, this occurs under practically the same conditions as,—and I believe it is partly a consequence of,—the proliferation of epithelium into lymphocytes in the lower line of the epithelium. Neither this migration nor this asserted mutation is seen in all areas. On the other hand, the latter in some places seems to have been so complete that the mutation has taken place even in the superficial layers. The usual interpretation put on this appearance is that the surface layers, or rather the whole thickened epithelial layer, has been desquamated, leaving the lymphocyte layer exposed. I do not believe that this explanation suffices to account for all the appearances noted in the examination of tonsils, though plainly it is seen to be the case in some; yet even

in these the question arises whether we have not to do with an artefact or with the result of trauma during the removal of the tonsil. I am constrained to believe that where the lymphocyte layer is thus exposed in acute exacerbations of chronic hyperplasia of the tonsil we have to do with a more or less complete transmutation of form at the point in question, at least in the majority of cases. I do not believe that phagocytosis by the lymphocytes has destroyed and removed the missing surface epithelium. When we come to study the phenomenon I have cited from Cordes we see that it is difficult,—I believe impossible,—to explain it on any other assumption than that the changed environment of chronic and the superimposed acute inflammation has wrought a transformation of the basal layers of epithelium in accordance with general biological laws, as applied to plants on the slopes of high mountains. The large mononuclear cells, plainly epithelial near the surface, gradually change their form as they stretch down a fibrous plane, sometimes almost seeming to invest it with a sheath from the inner layers of which fibres sprout. At any rate the protoplasmic exudates from these cells or fibrils may be seen interlacing with those of the fibrous stroma of the tonsil. I place no great stress on the karyokinetic figures which may be seen in these cells occasionally. That is incidental to the perturbation of the stimulus causing the inflammation.

While, as has been said, it is impossible for me to confirm from my own experience the origin of lymph nodes from a transmuted epithelial cell, I can testify to the formation of islands or nodules of small leucocytes or lymphoid cells with their supporting trabeculae ("Gitterfasern") within the epithelial layers of the tonsil in chronic hyperplasia. I am not quite convinced as to how they come there. Small leucocytes in clumps with intercellular network are not infrequently seen, while separately, as almost naked nuclei, they are frequently seen between the epithelial cells. Levinstein's surmise that these nodes are formed from lymphocytes which have penetrated from below and have become flattened into a semblance to the epithelium, but at the same time forming the young lymphoid cell there, does not appeal to me.

The revelations,³ unexpected as they are convincing, that the epithelial cell of adeno-carcinoma may suddenly change when transmitted by repeated inoculation of mice (a typical changing of environment) into a sarcoma cell, lends a force to these observations of Cordes as they strengthen the earlier heretical contentions of

3. Verhandlungen der Deutschen Gesellschaft, 1908, 12te Tagung.

Retterer.⁴ They furnish me also with a welcome support to an opinion slowly formed as the result of the cumulative observations of many years in the study of tonsillar histology.

Since the foregoing was written I have had occasion to make a report on the histological nature of a tumor from a case of Dr. Harmon Smith. The argument to be adduced from it has such a direct bearing upon the subject matter of this paper that I append it here as supplementary to it.

Lab. No. 4087, Cl. 526,369. Surgeon—Dr. Harmon Smith.

Nicolo Tomassino, act. 50. There is a large protruding hard mass springing from the region of the right tonsil. No glandular metastasis can be made out, though the growth is very extensive, involving the ramus of the jaw and most of the side of the pharynx. Marked pain or bleeding is not complained of and marked cachexia is not apparent.

The growth was first noticed four years ago by the patient. Two years ago a piece was removed for histological diagnosis at Roosevelt Hospital, and that of *epithelioma* was made. The external carotid near its distribution to the growth was ligated and the tumor was left untouched as inoperable. Four years having elapsed since the growth was first seen, and the history of the growth being as above, the clinical diagnosis of *endothelioma* was made at the Manhattan Eye, Ear and Throat Hospital. A piece was again removed for microscopic diagnosis. Though large enough for ordinary diagnosis, there are many points raised in its examination which can be settled, if at all, only by examinations of the periphery of the deep-seated portions of the growth.

How far the ligation of the nutrient vessels may be responsible for the present morphology of the growth it is impossible to say. If the tumor in this situation had not destroyed the patient in the first two years, or at least extended far beyond reach, being at that time supposed to be of an epithelial nature, it does not seem likely it could have then presented the ordinary clinical characteristics of an epithelioma or sarcoma of the tonsil. At any rate, even if the procedure has modified the structure of the growth in the two years which have elapsed since then, I think it presents none the less very instructive and interesting features.

It is made up of the proliferation of two morphologically sharply separated cells as seen in their atypical condition. One order of atypical cell, much the smaller in amount, manifestly

4. Retterer: De la Structure de la Cellule Epidermique et des Facteurs qui la Modifient,—Journ. de l'Anatomie et de la Physiologie,—XLIV, No. 6, Nov. and Dec., 1908. This is a more recent contribution to the same effect.

springs from and is a part of the surface epithelium. It presents many of the characters of a flat-celled epithelioma or canceroid. Cancer whorls or nests are seen in the surface-line of the epithelium itself. A few digitations of such atypical cells shoot down into the area of the atypical cells, making up the bulk of the growth, to be described later. In addition, there are separate islands and whorls of this epithelium in the bordering territory of the tumor proper. Were it not for the presence of adventitious cells of another character in overwhelming numbers beneath, there could be no question that all histologists would call this growth a *flat-celled epithelioma*.

Amid the flat-celled surface covering even where the cells are atypical, may be seen sharply differentiated clumps of cells, evidently transverse sections of pole-like digitations thrust from below towards the surface. These are cells of the bulk of the tumor mass below. At deeper levels these cells are merged into the lower line of the surface, and usually along the border line they are indistinguishable from the basal cells. Deeper down still there is a gradual departure from this resemblance, but there is no merging of the appearance of the deep atypical cells with those of the surface. One extreme is of a malignant epithelial type and the other is of a malignant connective-tissue type. Such continuity as exists between them is through cells resembling and usually indistinguishable from the basal cells of the epithelium. Just as there are places where the fairly normal-appearing basal cells of the epithelium merge into fairly normal flat-celled epithelium—itsself the origin of malignant canceroid-looking structure, as we have seen—so there are also such areas apparently giving rise to a mass of cells resembling large and medium-sized mononuclear lymphocytes and endothelial cells, with faint cell bodies and large round or oval nuclei. These are compressed in many places into polygonal shapes, and from these especially can be seen a cytoplasm giving origin to connective tissue fibrils, occasionally combined into large trabeculae dividing the growth into various-shaped compartments. Without examining the periphery of the tumor, it can not be positively stated that these cells furnish fibril exudates making up *all* this low-grade stroma. It may be safely said, however, that some at least of the fibrils from the tumor cells compose the stroma. Running through the sarcoma tumor cell masses are some single-walled capillaries, whose cells have nuclei longer than and cell bodies somewhat differentiated from the tumor cells; such capillaries do not seem to spring from or accompany the coarser trabeculae just spoken of as partly at least made up of fibrils from the tumor cells. In many places these capillaries and some few of the cells seem as though they might be

derived from the stroma beyond the periphery of the growth. In other places they closely resemble and seem to spring from the neighboring tumor cells. Some of the larger of these capillaries and some of the thicker-walled blood-vessels are seen to be invaded by the tumor cells which are mingling with their haematocytes.

The condition of the cells as to karyokinetic figures can not be made out in any of the cells, though evidently they are present in some of them, and a more careful hardening might have revealed them.

There are three ways of interpreting the appearance of this growth, which, of course, in its structure presents most of the ordinary evidence of malignancy:—

(1) We may regard it as a mixed growth. A malignant hyperplasia of the surface epithelium encroached upon and in some places invaded by a malignant hyperplasia of the endothelium of the lymph spaces, the two forms to a certain degree invading one another along a border territory roughly coincident with the basal cells of the epithelial covering, may be said to sum up one view of it—in other words, a combination of endothelial sarcoma and epithelioma.

(2) We may regard it as a malignant proliferation independently affecting two separate layers of epithelium.—in other words, a combination of flat-celled epithelioma and the basal-celled epithelioma of Krompecher.

(3) My own conviction is that we have here a revelation of the latent power of the basal cells of the epithelium to be transmuted into connective tissue or into flat surface cells under certain conditions. I regard the process as fundamentally one process; that is shown by the dynamics revealed in the clinical history. Neither sarcoma nor epithelioma of the tonsils or fauces runs any such clinical course as this,—why should a combination of them do so? This growth, in my opinion, started in a border domain of cells which under other conditions also exhibits evidence of being easily upset in its morphology by unknown molecular forces. A mild molecular disturbance has here occurred, which, if confined exclusively to the stroma, or exclusively to the epithelium, would not have been sufficient to cause cancer. Occurring here in cells with a tendency to mutation,—with an unstable equilibrium, in other words,—we have the combination exhibited by structure and by vital dynamics of a feeble potentiality. I do not see how any other hypothesis can satisfactorily account for the condition.