ON THE DYSONTOGENETIC ORIGIN OF BASAL-CELL CARCINOMA

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In 1933 M. Glasunow of the Oncological Institute of Leningrad published some observations concerning the origin of basal-cell carcinoma (Ueber das Wesen und die Histogenese der Basalzellenkrebses, Frankfurt. Ztschr. f. Path. 46: 140, 1933-34) which so interested us that we determined to set about their confirmation or refutation.

The "basalioma" or "basal-cell carcinoma," was first pointed out as a clinical entity by Jacob of Edinburgh in 1827, and as a histopathological entity by Krompecher in 1900. The latter insisted that the tumor arose from the basal cells of the epidermis, but in that he was strongly opposed by Borrmann, who adopted Cohnheim's theory and taught that the tumor originates from sequestered groups of ectodermal cells, and that any observed union with the epiderm is the result of subsequent growth, fusion, and commingling. Krompecher succeeded for a time in obtaining a large following, but as he attempted to apply the basal-cell theory of origin to tumors of the mucous membranes and internal organs, the enthusiasm waned.

Krompecher went so far as to declare that 75 per cent of all uterine cancers were of the basal-cell type, but Martzloff did not find a single instance among 387 cases that he examined microscopically, and Lansford and Taussig found no basal-cell tumors among 121 carcinomas of mucous membranes.

Owen examined 194 carcinomas of the tongue without finding a single basal-cell tumor, and later examined more than 500 carcinomas from the cavities and internal organs of the head, from the neck, esophagus, bronchi, cervix uteri, bladder and rectum, without encountering one that seemed to fulfill the requirements of the basal-cell cancer.

At present the term basal-cell carcinoma is rarely used except with reference to a fairly well characterized tumor of the skin, most frequent upon the face.

But Borrmann's theory of the origin of the tumors from "embryonal rests," although partly accepted by Ewing, has not met with general acceptance, and many, perhaps most, pathologists cling to Krompecher's theory that the tumor originates from the basal-cell layers of the epiderm. Some dissenters, however, are not without impressive names, or their theories without weight.

Haythorn, Walker and Johnson in England, Paul in Australia, and Mallory in America, believe that the starting point is to be found in
the cells of the hair follicles (tricho-epithelioma). Other writers, noting that the tumor, though common in man, is rare in lower animals, conclude that the hair follicles play no part in its origin. Ribbert, Ricker, Schwalbe and Adamson think that it arises from the glands of the skin (spiradenoma, syringoma, benign cystic epithelioma or epithelioma adenoides cysticum of Brooke).

The desire of each theorist to express and perpetuate his conception of the nature and origin of the tumor in a name has led to a lengthy terminology, almost impossible to correlate, as some of the terms are clinical—Jacob's ulcer, epithelioma exedens, rodent ulcer, epithelioma planum cicatriciale, epithelioma matilans, noli me tangere, etc.—and some histopathological,—adenogene carcinome (Ribbert), Retezellen-carcinom (Petersen), Matrixcarcinom (Petersen), carcinoid (Schmidt), carcinoma embryonale (Fabre-Domergue), basal-cell cancer, epithelioma

![Diagram](image)

FIG. 1. MERKEL’S DIAGRAM, SHOWING THE POSITION OF THE LINES OF CONCRESCENCe IN THE FORMATION OF THE EMBRYONAL FACE (BORMANN)

adenoides cysticum, Schweissdrüseneptitheliome (Ricker-Schwalb), tricho-epithelioma, spiradenoma, etc.

It is quite possible that several different but similar appearing tumors, of different distribution and of different clinical course, may be included under these various terms, and it is not impossible that different though similar appearing tumors may arise from the same source. But to regard either as more than a possibility is unwise. The investigators quoted arrived at their different conclusions, not through any demonstration of the facts, but because some of them believed that they saw the tumor cells arising from the basal-cell layers of the epiderm, or from the hair follicles, or from the sweat glands, with which they certainly and frequently appear to be in intimate relation, while others saw in the same intimate relationship no more than the invasion of these structures by tumor cells arising elsewhere.

Great caution should always be exerted in drawing conclusions from the proximity and intermingling of normal cells and tumor cells, for such reasoning may be fraught with implications not at first suspected. If, as the result of the careful study of a large section, one succeeds in finding a point at which the cells of the tumor, through their situation and morphology, appear to be definitely related to and arising from a hair follicle or a sweat gland, and concludes that, therefore, the tumor originates from one or the other of those structures, he implies that he
is seeing the point at which the tumor began, although it may have been in existence for years and have invaded and destroyed many hair follicles and sweat glands. If he has found several such points, and drawn the same conclusion, he implies that the tumor has, and has had, numerous successive or continuous beginnings extending through all those years to the present time. It should scarcely be necessary to say that the only time at which the precise origin of a tumor can be determined is before it reaches visibility, which is, of course, before its existence can possibly be known.

The very fact that the origin of the tumor is ascribed to such different sources as the basal cells of the epiderm, groups of ectodermal cells isolated from their normal environment during embryonal development, hair follicles, and sweat glands, is not without significance. Indeed, it suggests that it probably does not arise from any of them, but from something more primitive in nature and possessed of developmental energy capable of producing any or all of them.

Residual sequestered embryonal cells such as were predicated by Cohnheim would amply meet such a requirement, for it is conceivable that, had they had the opportunity to fulfill their normal destiny, they might have developed into epiderm, or any of its appendages, but having been prevented from so doing by the accident of dysontogenesis, they give origin to this or that type of structure more or less closely approaching one or other of the normal types without perfectly corresponding to any. In this manner may be explained the variations in histological structure that have resulted in the bewildering terminology. But it is not our intention to make this hypothesis so far-reaching as to lead the reader to conclude that we believe all of the tumors described under the various names given them by the different authors to be one and the same thing, with slightly different appearances and manifestations. There may be different tumors of different origin but close
resemblance that are confused with one another, as will be pointed out later.

The histological peculiarities are, however, by no means the only ones shown by the peculiar tumor or group of tumors called basal-cell carcinoma. Clinically this tumor is characterized by occasional multiple occurrence, long duration, slow growth, anatomical distribution almost limited to the face, complete or almost complete absence of metastasis (Spies has reported three cases with generalized metastasis), and an astonishing susceptibility to such destructive agents as carbon dioxide snow, arsenical pastes, x-rays and radium.

It is also interesting to observe that with all of the successes that have followed the application of carcinogenic agents, such as tar, to the skins of the lower animals, no basal-cell tumors have ever been recorded. All of the experimental tumors are prickle-cell tumors with cornification.

![Fig. 3. Glasunow's Plotting of 99 Cases of Basal-Cell Carcinoma](image)

The diagram to the left shows the position at which the patient indicated the starting points, that to the right the position of the tumors when the patient applied for treatment.

The rarity of the tumor elsewhere than upon the face, and the difficulty of accounting for this restricted anatomical distribution became a matter of particular interest to Glasunow, who decided to investigate it with the view of obtaining some light, if possible, upon its origin. He therefore collected 254 cases of basal-cell carcinoma of the face, confirmed the diagnosis by histological examination in 117, and, finding the exact site of occurrence was carefully stated in the protocols of 99, proceeded to plot their localization. Two of his diagrams, dealing with single tumors only, are shown in Fig. 3. The first indicates the positions in which the patients stated that the tumors had originally made their appearance; the second, the positions they occupied at the time the patients came to the Institute for treatment. Numerous other plottings given in his paper need not be reproduced here, as they all show substantially the same distribution. Glasunow is convinced that the distribution of the lesions so closely corresponds with the position of the "facial fissures" or intervals between the various embryonal processes or buds through whose final concrescence the face is formed,
as to prove that the tumors are of embryonal origin and dysontogenetic. He believed that this opinion was confirmed by the way in which the tumors first made their appearance. Of 99 histologically confirmed cases, 35 or 36 per cent arose from small antecedent lesions spoken of most frequently as "warts" or "pimples," only 9 of which were of less than one year's duration, 27 from one to five years' duration, while the remainder had existed from five to twenty-five years, except for 8 that were present at birth. Of the 71 cases described as beginning in "warts" or "pimples," 32 seemed to have begun their neoplastic development after some kind of traumatism, as scratching, removal, or cauterization. In 15 cases the lesions were thought to have begun in "sores" (ulcerations?) and 11 were said to have resulted from injury.

At this point it may be well to insert the conclusions with which Glasunow ends his paper and which form our starting point:

1. The tumor of the skin designated by the greater number of au-

thors of the present day as basalioma or basal-cell cancer of Krompecher, is peculiar to surfaces with ectodermal coverings, and in an overwhelming majority of cases develops upon the face.

2. The peculiarity of these new growths is to be found not only in their histological structure, but is shown also in their slow course, superficial destructive growth, absence of metastases and cachexia, and their marked susceptibility to numerous destructive agents.

3. No one has yet succeeded in producing such tumors experimentally.

4. The manifold histological differences between different tumors permit the conclusion that the starting point of the tumors is to be found in some multipotent embryonal material.

5. The almost complete coincidence of the points of origin of the tumors with the lines of fusion of the facial buds is the best indication of their dysontogenetic nature.
6. The peculiarity of the tumors should find expression in some appropriate designation. That of “basal-cell cancer” is unsatisfactory.

7. In consideration of the special characteristic peculiarities of the tumors, it would be better, and more correct, to call them facial fissure carcinoids or skin carcinoids.

It was decided to put these interesting results to the test, and Dr. Ciccone at the Oncologic Hospital and Dr. Gelehrter at the Philadelphia General Hospital agreed to cull out of the case histories and histological material of each institution an equal number of cases to be plotted upon identical diagrams of the face.

It was agreed that only those cases classified in the hospital records as basal-cell tumors could be used, and that no case should be plotted until its histology had been carefully checked. Practically every tumor was checked by two of the authors.

Several serious difficulties soon presented themselves.

1. Exactly what is the histology of basal-cell cancer?
2. How nearly can one approximate the point of origin of a tumor by what the patient says or by inspection of the developed lesion?
3. How nearly is it possible, upon the developed face, to determine the lines of embryonal concrescence?

(1) The histology of the tumors identified as basal-cell cancers is subject to considerable variation according to the personal equation of the pathologist. Ordinarily this may make little difference, but when it becomes important to make accurate estimation of some scientific principle such as is concerned in Glasunow’s theory of origin, or to make comparisons of different methods of treatment, some criteria must be adopted that will make it reasonably sure that as nearly as possible the same things are being compared.

With the basal-cell cancers the establishment of such criteria becomes difficult because of their variability which has to do (a) with the
complete independence of the basal-cell type or its association with the prickle-cell type of tumor, the latter being frequent and transforming the tumor from a purely local to a metastatic type of growth; (b) with the shapes of the cells, which are sometimes cuboidal, sometimes whetstone shaped, sometimes distinctly fusiform, and sometimes elongate fusiform; (c) with the occasional occurrence of parakeratosis in and among the cells; (d) with the occasional occurrence of what resemble prickles on all or the greater number of the otherwise typical basal cells; (e) with uncertainty as to whether the epithelioma adenoides cysticum of Brooke should be included among the basal-cell tumors or excluded from them, and if so why? It was finally decided to consider only those tumors that had already been identified as basal-cell carcinomas by others, to reject any among them that varied widely from our conception of basal-cell carcinoma, to adopt the criterion of Ew-

![Diagram of facial distribution of sequestration dermoids](image)

**Fig. 6. Distribution of the Sequestration Dermoids of the Face (Forgues)**

...that “the normal transformation into squamous cells entirely fails”, and to reject every one in which prickle cells or parakeratoses were found among the basal cells.

(2) The difficulty of plotting the exact positions of the tumors must have been keenly felt by Glasunow, as he presents his diagrams in pairs, one showing the position at which the patient first saw the lesion, the other its position when the patient applied for treatment at the Institute. Dr. Gelehrter, who plotted the cases in the Philadelphia General Hospital, has represented his tumors as small and at the site of origin; Dr. Ciccone plotted those of the Oncologic Hospital as they appeared when the patient came to the hospital.

(3) The development of the human face is explained in every textbook of embryology and its principles are easy to understand, but though the particular process by which the different features are formed and the lines of concrescence by which they are united are shown in many diagrams, their exact position upon the adult face and the amount of leeway one can assume with respect to accidents of development is uncertain. Can a small defect taking place during concrescence be

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1 Neoplastic Diseases, Ed. 3, 1928, p. 513.
pushed this way or that during subsequent growth or must it remain in the exact line? Is it more apt to be in the exact line when the subsequent growth is restricted and to be pushed out of the line where growth is more massive?

Mr. Irwin F. Faber, instructor in drawing in the department of Pathology in the School of Medicine of the University of Pennsylvania, furnished the diagrams of the face used for plotting, and it was decided to use Merkel’s diagram of the position of the facial fissures which we borrowed from Borrmann as the standard of distribution (Fig. 1).

The results of the plotting of the cases from the Philadelphia General Hospital and the Oncologic Hospital are shown in Fig. 4.

Before arriving at a final conclusion with respect to the correspondence of tumor distribution and fissures, it seems advisable to compare the results with two other lesions for which similar dysontogenesis is supposed to be responsible, viz., the so-called inclusion or sequestration dermoids and the so-called mixed tumors of the face.

![Fig. 7. Distribution of 75 Mixed Tumors of the Face Collected from the Literature](image)

Instead of collecting the cases scattered through the literature, we have borrowed the diagram representing the distribution of the dermoids published by Forgues in his Précis de pathologie externe. This is shown in Fig. 6.

It so happened that the senior author had recently reviewed the entire literature of “mixed tumors of the face”, and was, therefore, able to amplify the plottings of Moulonguet and Peynet by the addition of about 75 later cases of mixed tumors of the cheeks, lips, nose and supra-orbital regions (Fig. 7).

The results of the three plottings may at first appear somewhat vague; but upon more careful consideration the great majority of the lesions in each case are seen to center about the facial fissures, and the number of aberrant cases in one series is not greater than in the others. It therefore seems to us that the basal-cell carcinomas do show a distribution capable of being interpreted as the result of a dysontogenetic origin from the embryonal facial fissures.

But what of the distribution of other skin cancers of the face?
they too found to collect about the embryonal fissures? In order to settle this question, a similar and independent plotting was made with an equal number of cases of squamous- or prickle-cell tumors from each of the contributing institutions, done in the same manner, by the same men. The result is shown in Fig. 5, and it is at once evident that the squamous-cell cancers occur in a distribution that has no relation to the embryonal fissures. It is difficult to believe that tumors of such entirely different distribution can have the same origin, and our studies therefore seem to support the hypothesis of Glasunow.

Remarks

It goes without saying that the occasional occurrence of basal-cell carcinomas upon the upper part of the forehead, and their rare occurrence in other regions where there is no concrescence of embryonal buds to account for them, are opposed to the theory under discussion. But a glance at Forgue's diagram of the distribution of the dermoid cysts shows corresponding exceptions. How can these exceptions be accounted for?

Such occasional aberrant cysts and tumors do not seem to be of sufficient importance to throw discredit upon the theory. They rather remind us of something pointed out before, namely the difficulty and sometimes the impossibility of being certain of the nature of all of the lesions under consideration. As sequestration dermoids may not always be certainly differentiated from sebaceous cysts, those shown in the diagram to be on the forehead may not have been dermoids, but sebaceous cysts mistaken for them, and therefore not to be classed with dysontogenetic lesions. In the case of the basal-cell tumors it is quite possible that the few found upon the forehead and scalp, and any others remote from the region of the facial fissures, were not the carcinoma basocellulare they were thought to be, but some other tumor—carcinoma adenoides cysticum, for example—of different origin.

Conclusions

A substantial number of carefully selected and histologically confirmed cases of basal-cell carcinomas from two different hospitals have been plotted upon two diagrams of the human face in order that their distribution might be studied with reference to their possible dysontogenetic origin through defective concrescence of the embryonal facial fissures as suggested by Glasunow. The results have been compared with the plantings of other supposed dysontogenetic lesions, sequestration dermoids, and mixed tumors, with the result that all three types of lesion are found to conform to about the same anatomic distribution, which is entirely different from that of the more common squamous-cell or prickle-cell carcinomas. We do not believe that our observations settle the question, but we do believe that they support the theory of Glasunow that the basal-cell carcinomas are dysontogenetic tumors which originate in imperfections in the closure of the embryonal facial fissures.