# MORPHOGENESIS AND HISTOMECHANICS OF THE BENIGN CONNECTIVE TISSUE NEW-GROWTHS OF THE SKIN*

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Among the benign connective tissue neoplasms of the skin various forms have been grouped together. This is undoubtedly the result of different criteria for their differentiation by clinicians and pathologists, and to the various morphological aspects presented by these new-growths. Thus, along with vascular and muscular neoplasms *histiocytomata* (Woringer (1), Diss (2)), *recurring dermatofibromata* (Darier-Ferrand (3), Hoffmann (4)), *fibromata* (Unna (5), Civatte (6)), *xanthomata* and also, both because of their morphology and because of particular views on their histogenesis, *neurofibromata*, *neurinomata* (Mosto (7), Stewart-Copeland (8)) and *sclerosing angiomata* (Penner (9), Evans (10)) have been described and classified as self contained units. Other authors like Stout (11) have applied to a great part of these neoplasms the more generic term of mesenchymomata. These different classifications have also been due, to a large extent, to the various theories about the morphology and the embryology and histogenesis of connective tissue.

Our aim has been to study the morphokinesis of these new-growths in order to find out what the structural arrangements of these forms are like, and what, if any, are the relationships binding the elements (cells, fibers, vessels) of their make-up. The third problem was to go back from these data to the histogenesis and differential diagnosis between them and other new-growths of the skin of similar morphology.

## MATERIAL AND METHODS

The material observed derives from the specimens of the Institute for Pathological Anatomy of the University of Bologna. To the differential diagnosis of the various forms we have applied the morphological criteria reported by Stout (11, 12, 13); Evans (10); Masson (14); v. Albertini (15). In defining the different cytological forms of connective tissue we referred to the classical criteria of Aschoff; Marchand; Maximow; Policard.

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Out of 25,000 specimens we have isolated 53 benign connective tissue new-growths of the skin, among which there where 31 dermo-fibromata, 22 histiocytomata.

Apart from the examination of this series of cases with the common routine methods of histology (hematoxylin-eosin, Masson, Van Gieson, silver impregnation, study of fats, Turnbullblue, etc.) we have selected for special treatment several cases which were characteristic for each type of new-growths, totaling 16 observations. The material was embedded in paraffin and serial sections to the extent of about 200 for each case were prepared. These sections were colored after the procedure of Hotchkiss-McManus and contrast-colored with hematoxylin-erythrosin-tincture of saffron. By this method the cytoplasm of the cellular elements and muscle fibers take on a rose hue, the nuclei are dark purple, the collagenous fibers intensely yellow, while the reticular fibers, the hyaline membranes and the PAS positive elements are intensely red. In the so-colored sections the elastic fibers were examined exploiting their property of primary fluorescence which remained unaltered. To reconstruct the structures three-dimensionally a microphotographic method was employed with an enlargement from 80 to 240 times. The negatives prints were made on 208 B "Ferrania" paper and, as to the stronger magnifications, also on positive "RECTA ultra-contrast FERRANIA" film.

## HISTOLOGICAL AND MORPHOKINETIC PICTURES

The histological features of the different new-growths may, from a merely qualitative point of view, be grouped in one common description. These new-growths have no capsules and merge with the surrounding skin which is being infiltrated by them. Their seat is always in the dermis of the skin and particularly in its deeper layers. Employing a small magnification, a fascicular structure of fibrocellular bundles running in all directions can constantly be observed. Storiform arrangements, figures of whirlpools and fan-shaped tassels may be discerned. (FIG. 1). Very frequently a fishbone-like figure is met. These structures consist of cellular elements, vessels and

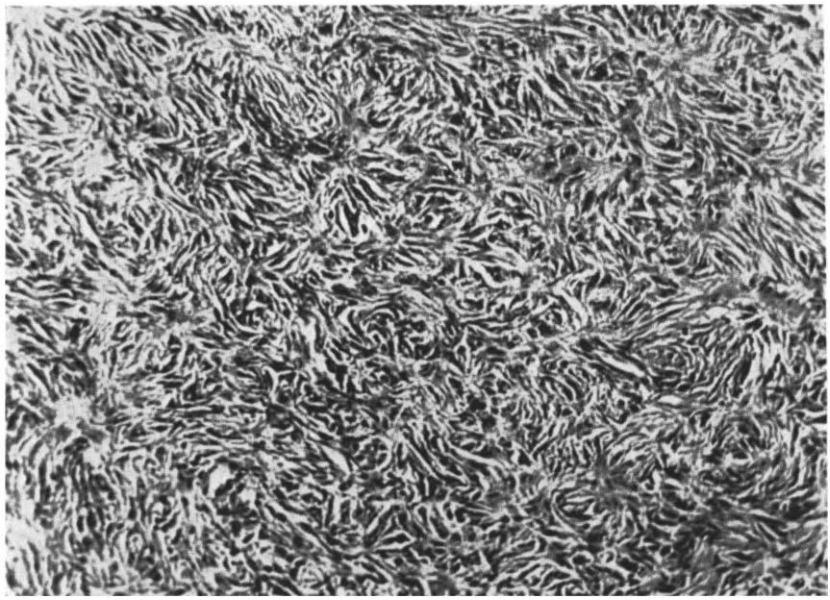


FIG. 1. "Characteristic features of the new-growths: the cellular groups take a storyform arrangement, while in some points the vasculo-stromal axis becomes collagenous. 'Sclerosing angioma'." PAS-Hemat.-Safran 200×.

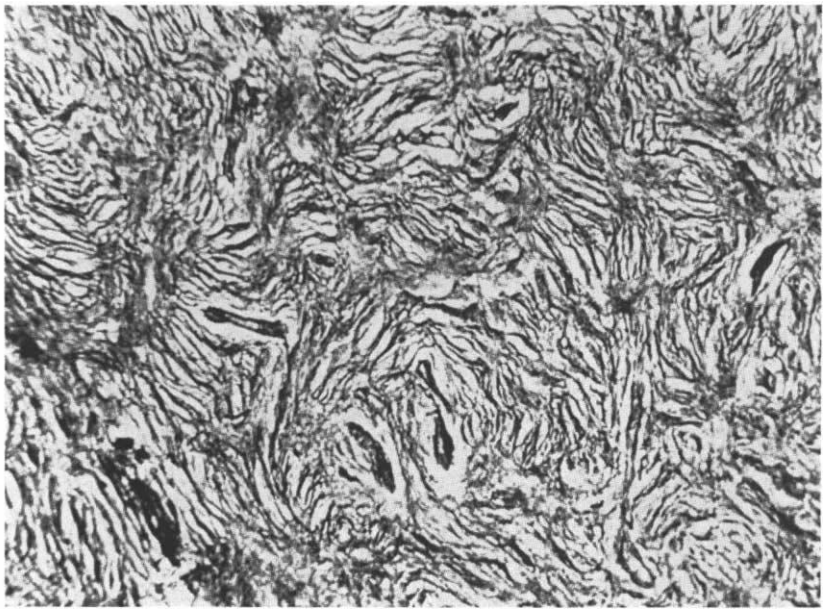


FIG. 2. With the silver impregnation the star-like and fish-bone like features appear more evident. Pap-Bielschowskj 200×.

a stroma. (FIG. 2, 3) The cells are of two prevailing types, fibrocytes and histiocytes. In some forms the first type of cells predominates, in others the second one. Finally, there is a third group containing an equal quota of the both types of cells. Except in very rare cases the histiocytic elements are never quite absent. A frequent feature is the accumulation in the cytoplasm of the histiocytes of lipids showing primary fluorescence, hemosiderin pigment etc. In some cases

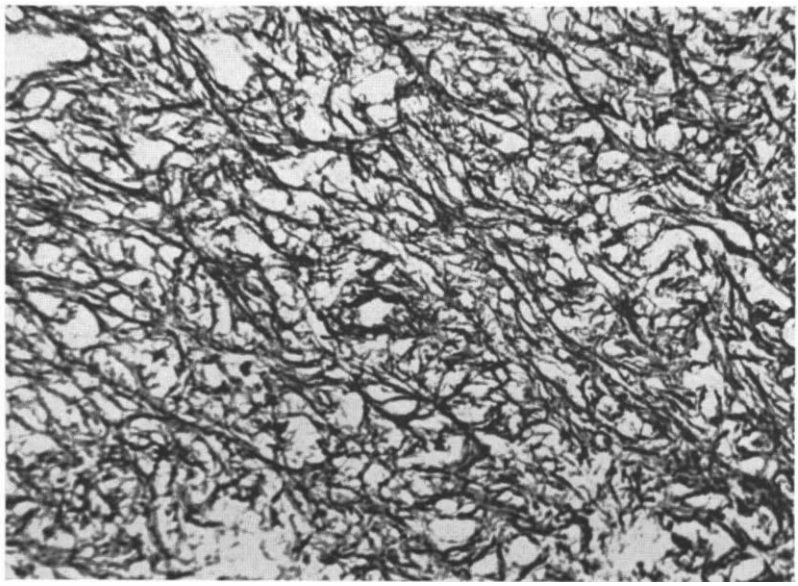


FIG. 3. "The silver impregnation of a 'sclerosing angioma' shows, near the alveolar structure of the reticular fibers, some sclerotic bundles in connection with the vessel wall." Pap-Bielschowskj 200×.

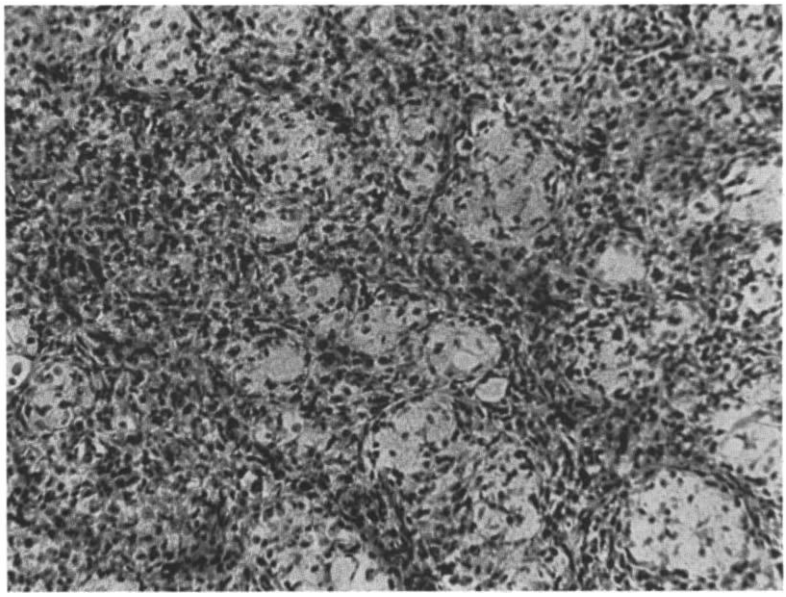


FIG. 4. "Fibroxanthoma: alveolar arrangement of a group of foam cells." PAS-Hemat.-Safran 200×

with predominating histiocytes, polynuclear giant elements can be observed, always in a close contact with the vessel wall. The vessels are nearly always very numerous; they are principally of three types:

1) The slit-like or lacunar type, by which we mean slender cavities, sometimes provided with endothelium but, more frequently, delimited by the proliferating elements themselves.

2) Small vessels with well-defined walls.

3) Arterial and venous supply vessels.

The first two types show a varying caliber and are always intimately mixed up with the proliferating elements. The stroma which though

more or less abundant is invariably present, consists both of recticulin and collagen. The reticular tissue is found prevalent in new-growths in which phenomena of intense proliferation are observed; collagen, on the other hand, predominates in forms with more stable elements, *i.e.*, where proliferation is less active and is accompanied by a smaller number of cells. (Fig. 5)

The examination of the serial sections and the successive plastic reconstruction in space of the 16 selected cases has shown that these new-growths are characterized by a fundamental feature. This is represented by an aggregation of cellular elements and stroma in a bundle around an axis or vascular stem. Such an arrangement seemed to us to resemble the structure of an "ear of corn." The cells are always in contact with the vascular stem and appear to be continuous with the elements of the periadventitia of the vessel lumen. The architectural plan of this structure is identical through-out all the examined new-growths; it seems, indeed, the real elementary constituent of these neoplasms. This elementary formation (bundle of cells with central vascular stem) however, can be subject to modifications depending: 1) on the degree of collagenization (quantitatively or qualitatively); 2) on the morphological differences between the cellular elements and the abundance in cells of the bundle itself; 3) on the caliber of the vessel lumen, the thickness of the vessel wall and the quantitative relationship between the vessel and the quota of cells in the bundle.

As a matter of fact the bundle may, sometimes, no longer be easily recognizable because of its complete fibrous transformation. In other cases, however, in new-growths with predominating histiocytes, the bundle may be extremely small and short. The lumen of the central vessel is sometimes reduced to a simple slender slit; in such cases only a delicate reticular knit-work can be seen and the fascicular aspect becomes disguised. Between these two extremes there is a situation where the bundle formation ("ear of corn" type) is most rigidly pronounced. One observes it most frequently in the so-called dermatofibromata. There we find the central stem provided with a modest quota of fibrils on which are spokewise inserted the elongated cytogenic elements. The dimensions of the bundle are conditioned, above all, by the number and size of the cells. The bundle is, as we said previously, smallest in size in predominantly histiocytic new-growths. In purely fibrocytic forms, (*e.g.* desmoids), the bundle can assume very conspicuous dimensions and become downright visible to the naked eye. In such event a large bundle can be seen to branch out into smaller units (elementary bundles).

The central vessel may be represented by a

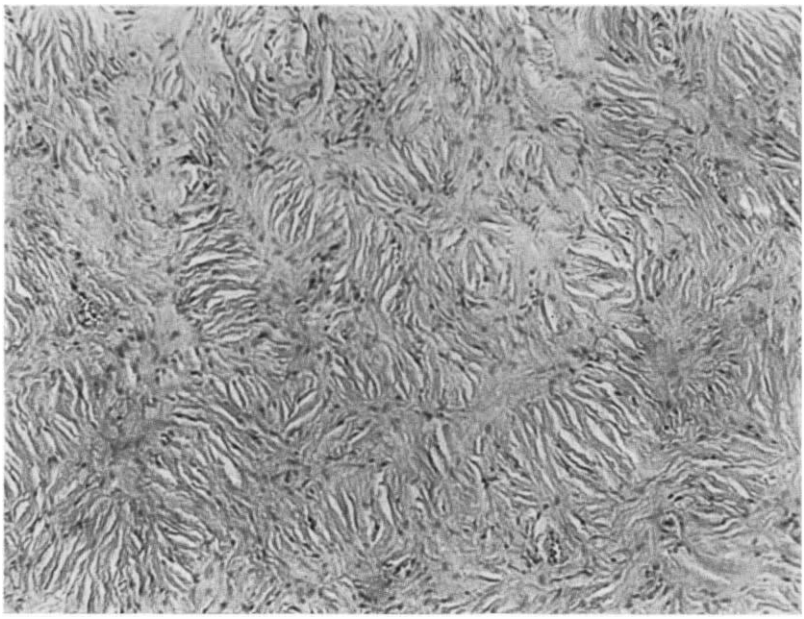


Fig. 5. "Sclerosis of a dermal fibroma; the fascicular structure is definitive." PAS-Hemat.-Safran 200×.

thin slit, a feature seen in the smallest bundles. In bundles of more conspicuous dimensions the caliber of the central vessel increases, while the vessel walls appear more complex and better defined.

Among the most frequent general morphological features of these new-growths there are "star-like" and "fishbone-like" figures and besides the alignment of the nuclei in a row. (Fig. 6) The "ear of corn" type of bundle structure accounts easily for these features. When the bundle is transversely cut, it will present the shape of a star, in case of a longitudinal section it will appear like a fishbone figure. The nuclei will be aligned in rows, if they have been cut longitudinally parallel to the bundle axis and are lying all on the same plane. A typical feature of these new-growths is the vortex. Much emphasis has been laid upon this feature by many authors; some of them have grouped several types of these new-growths basically because their common and most outstanding characteristic has been the vortex (vorticoid tumors of Bednar (16)).

We have been able to observe from our examination of serial sections that the vortex is a secondary feature dependent on the posture of the bundles and their mutual relationships. The vortex can be produced under the following circumstances: 1) folding of the bundle upon itself; 2) the meeting at a propitious angle of two or more bundles; 3) ramification of a bundle. The particular arrangement of the nuclei observed at the level of the elementary formations is due to the "spiral" mode of implantation of the cellular elements in relation to the central vascular stem. We found, that the nuclei are never aligned in a palisade-like way or parallel to an axis but always arranged in undulating lines (like spermatocytes in a seminiferous duct). Another interesting characteristic which can be well seen in bundles with a better recognizable structure, is that the distance between two stems does not transcend a certain limit *i.e.* remains almost constant. When this distance becomes larger, as, for instance, in the center of a vortex, we have noticed the setting up of a new branch by the preexistent bundles, sometimes represented by a newly formed vascular bud. On the basis of these observations we are convinced that the vasculocellular elementary bundle meets those structural conditions which characterize an anatomical morpho-functional unit, *i.e.* a unit or elementary organ in the sense of (17) (as a glandular acinus, or an intestinal villus). Some features of these new-growths, however, do not seem to fit easily into the strict structural scheme which we have described.

Such morphological features are seen above all

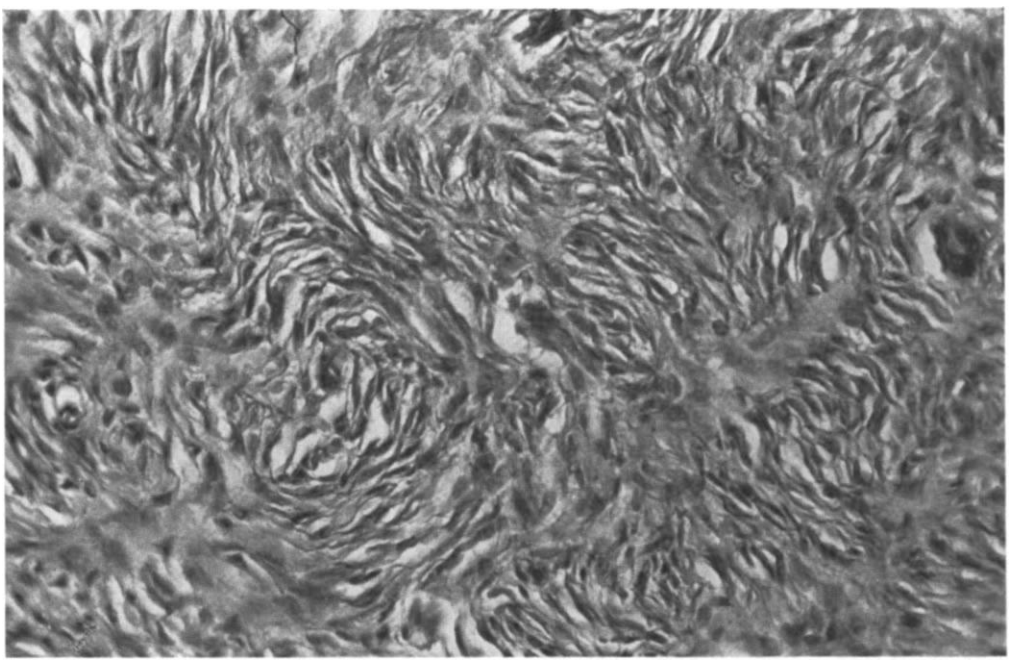


Fig. 6. "Large whirlpools forming; the vascular stems are represented by multinuclear elements with evident cavities." PAS-Hemat.-Safran 225×.

in new-growths with a particularly developed vascular network so that the new-growth acquires an angiomatous aspect (FIG. 7) and, on the contrary, they are not recognizable in those featuring extreme collagenization with a notable rarifaction of both the cellular and chiefly, the vascular element. An explanation of these aspects, as far as the angioma-like structures are concerned, may be found in an observation which we were lucky enough to make, of several cases in which we found angiomatous features beside features of fibrocyto-histiocytomatosis (the latter form more frequent). Between these extremes there was a series of pictures where the participation of both components in a varying degree could be observed.

With regard to the second possibility, concerning forms with a marked collagenization, we were able to see, beside areas of fibrocytomatosis with considerable vascular and cellular development, zones with a progressive falling-away of both components. They were replaced by considerably increased metaplastic elements, ending up in a sclero-hyalinosis of the bundle itself.

These data have suggested to us the hypothesis that those different aspects have a common matrix which is always represented by the above-mentioned vasculo-connective-tissue unit with the possibility of more exuberant development of either the connective tissue or the vascular element. (Text FIG. 1)

These modifications which, as it was said before, consist morphologically in a greater or lesser collagenization, in upward or downward variations of the vascular component, in a more or less marked tendency towards cellular proliferation, have been interpreted by us in a morphokinetic way. We assume that these phenomena are the result of a process of "structural re-arrangement," by which we intend to describe the gradual replacement of old bundles by analogous units of more recent origin. The still fertile cellular quota of a vasculo-cyto-stromal unit tends, in fact, to form a new unit which modifies and reorganizes (with mutual interaction) the preceding structures. This "re-arrangement" is observed more frequently and with greater clearness in cases in which proliferative phenomena are more outstanding, *i.e.* in types of a predominantly histiocytic participation. In the latter we have seen that the vascular structures are frequently represented by "slit" formations. The cells covering these formations appear sometimes to be derived from the elements of proliferation themselves.

Only in the more mature bundles there are small vessels with well-defined walls. The latter aspects, however, are very rare, for, when the

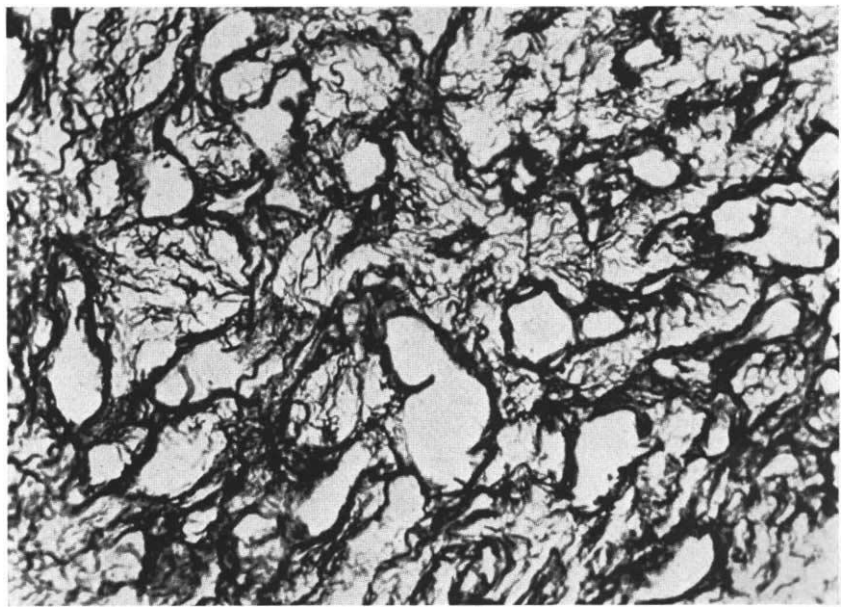
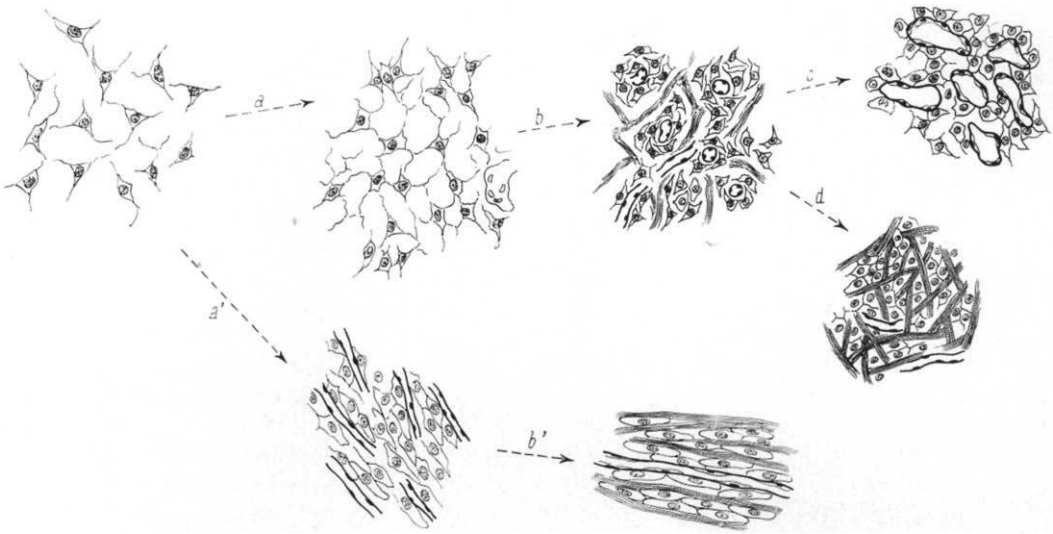


FIG. 7. "Vascular area of a new-growth. From the vessel-walls a great deal of fine reticular fibers bounding the cellular bodies departs." Pap-Bielschowskj 400×.




TEXT-FIG. 1. The illustration shows schematically the morphokynesis of some new-growths of the connective tissue.

Out of a mesenchymal, not yet differentiated tissue one gets in *A* a first attempt of organisation, similar to a very young granulation tissue; in *B* the proliferation of the histiocytic cells forms little whorls with a central capillary vessel (sclerosing angioma). This tissue may produce typical angiomas (*C*) or scar-like nodules (*D*) (histiocytoma spent-type).

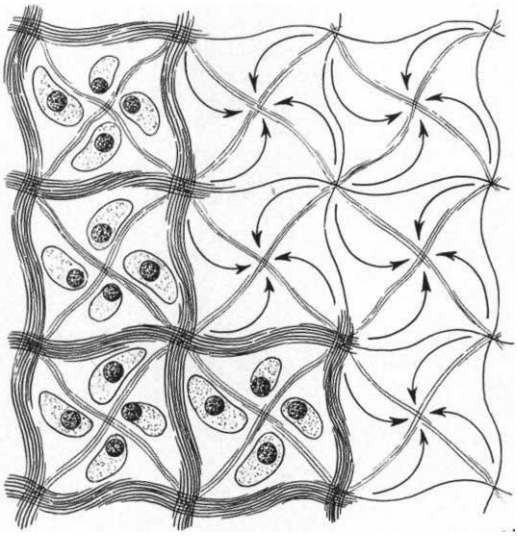
On the other hand sometimes mesenchymal elements set in elongated fibrocellular bundles in direct connection with capillary vessels ($A_I$). They become frequently fibrous and hyalinized ($B_I$).

quota of fibrils and stroma of the bundle predominates, the vessel becomes obliterated. The process follows the same ways which lead to the formation and obliteration of the capillaries in the medullo-vascular area of the embryo (Thoma (18)). Such stages present themselves also in the evolution of granulation tissue in a scar (Hueck (19)). Simultaneously with the complete collagenization of certain bundles with obliteration of the small central vessel, we have observed a proliferation of elements of the periadventitia of the main vessels which become organized into new bundle formations. This is evidenced by the formation of protoplastic buds, which become hollow inside and by small groups of cells organizing themselves in order to enclose a new thin fissure. It is precisely those new structures which modify the preceding architecture and reshape it continuously around the new points of proliferation they represent.

When one succeeds to hit upon an appropriate moment in such "re-arrangement" one notices the interlacing of the designs of the already collagenized bundles with those of the younger elementary units. The new bundles arrange themselves to surround the older ones and at (Text FIG. 2) the same time appear surrounded by the latter. It should be noted that the axis of the newly formed bundles are never in the same plane as those of the collagenized ones. This arrangement has been described by many authors (Penner (9); Evans (10); Rather (20); Ewing-Powel (21)) under the term of sclerosing angioma. We believe this to be a mistake; actually, that which has been interpreted as endothelium of the angiomatous formation, is nothing else but the outline of the new units, and what has been regarded as the sclero-hyaline wall of the new-growth is, in fact, the old already collagenized unit. A particular feature confirming this view is the presence of reticular connective tissue disposed around the collagenized bundles in close contact with the newly formed units.

Let us recall and emphasize that be it the stage of proliferation or the stage called "sclerosing angioma" or the third type with already collagenized elements (which we call the "spent type"), they are morphogenetically uniform, representing the evolutionary stages of the same new-growth which passes from a flourishing phase to one of complete collagenization.

The structure based on elementary units remains preserved even where there appear elements with a distinctly foamy cytoplasm (xan-



TEXT-FIG. 2. It shows the "remanagement" process which appears in the "histiocytomata." In the old collagenizing net-like structures, new cellular elements proliferate and put themselves in order forming little whorls.

thomatous cells) or with an accumulation of iron or fluorescent substances (probably lipoproteins). In fact, the xanthomatous transformation either strikes the cells of the vasculo-cyto-stromal unit entirely, or spares them wholly.

The study of morphokinesis has also permitted us to differentiate these new-growths from other ones, closely related to them from a morphological standpoint. We are referring above all to new-growths of the skin of nervous origin, which many authors (Mosto (7); Stewart-Copeland (8); Zack (22)) associated, at least from a histogenetic point of view, with the group of neoplasms studied by us. The similarity is due to certain morphological aspects, especially to such features as storiform, fan-like, whirlpool figures and the alignment of nuclei in palisade-like form. We have already seen that the first three aspects depend upon special arrangements and reciprocal adaptation of the elementary bundles. Attentive examination has further revealed that in the new-growths which we have studied, an arrangement of nuclei in palisade formation does not occur, but only an alignment in undulating lines. This is due to the different structure of the elementary bundle in connective tissue and nervous tissue tumors. In the former there is the arrangement in "ear of corn" fashion with helicoidal implantation of the elements of the new-growth on a vasculo-stromal axis; in the latter we have a structure of syncytial lamellae wrapped cap-like in a stroma containing the vessels.

## CONCLUSIONS

It emerges out of our research that the group of new-growths we studied presents common structural characteristics. They are based on the arrangement of elementary units of bundle form, composed of a central vascular stem in association with cells and stroma.

It follows:

1) The different morphological features are exclusively due to various combinations of the bundles among each other, to the "re-arrangement" of single bundles and to the predominance of one constituent over the other within the bundle.

2) The strict structural arrangement in anatomical elementary units indicates that the morphological foundation of these new-growths is of an organoid type, a fact that raises doubt about their neoplastic nature as tumors (Butenandt (23); Buengeler (24)).

3) The strictly morphological limits of our research do not allow us to indicate with certainty the histogenesis of these new-growths.

We incline towards the assumption of a common germinal cell capable of development both into an angioblastoma and connective tissue, for the following reasons: because in all these new-growths histiocytes are present; because in the vasculo-cyto-stromal unit, especially those of more recent origin (the actively proliferating forms) the vessels, stroma and cells are in a close relationship of continuity and, finally, because of the way in which the "re-arrangement" of the new-growth takes place.

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