

ON THE PRESENCE OF NEW ELASTIC FIBRES IN TUMORS.

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PLATES VIII AND IX.

The question of the participation of elastic fibres in the hyperplasia of connective tissue has recently aroused a good deal of attention, especially since the discovery of differential stains has made possible the recognition of very delicate elastic fibres. Sclerotic blood-vessels seem to have been first and most extensively studied, with a view to ascertaining not only the fate of the elastic fibres in the media, but also the nature of the newly-formed fibres in the intima. Langhans¹ was the first to declare that this new tissue consisted largely of elastic fibres, and later Baumgarten² and Heubner³ confirmed this view. More recently Dmitrijeff⁴ and Jores,⁵ working with better staining methods, have described in detail the processes occurring in arteriosclerosis. Though they find minor differences in the syphilitic and non-syphilitic forms, the process in the main is found to be the same in all, namely, a granular disintegration and final absorption of the elastic fibres of the media followed by an extensive proliferation of elastic fibres in the intima. The thickened intima, in fact, consists almost wholly of delicate elastic fibres.

Both Jores and Dmitrijeff consider that the growth of these fibres in the intima is compensatory, to make up for the loss of elasticity in the media, but they differ in opinion as to the rapidity of their for-

¹ Virchow's *Archiv*, 1866, xxxvi, p. 201.

² Virchow's *Archiv*, 1878, lxxiii, p. 90.

³ Dieluetische Erkrankungen der Hirnarterien, Leipzig, 1874.

⁴ Ziegler's *Beiträge*, 1897, xxii, p. 207.

⁵ Ziegler's *Beiträge*, 1898, xxiv, p. 458.

mation. Dmitrijeff finds them always in the older parts of the tissue and thinks they are the result of a slow chronic process, while Jores finds them appearing in the very early stages of endarteritis proliferans. This opinion is confirmed by recent researches of Czyhlarz and Helbing.⁶ Jores believes that endarteritis proliferans should not be classed as a chronic inflammatory process, since it differs from such in any other tissue in this one important characteristic, the production of elastic fibres instead of white fibrous connective tissue. The hyperplastic connective tissue which results from chronic inflammation in other tissues, does not, according to his view, ever consist of elastic fibres. This assertion is disproved by the recent investigations of Melnikow-Raswedenkow.⁷ He seems to be the first who has systematically studied, by Weigert's staining method, the normal distribution of elastic fibres and the question as to their increase in different pathological processes. His investigations include the liver, spleen, lymphatic glands, heart, adrenal, and testicle. His conclusions are as follows: In hyperplastic connective tissue there is in almost all cases a proliferation of elastic fibres. This proliferation is always compensatory in character, either to make up for a loss of elasticity in the organ, or to increase its normal elasticity. Thus in cirrhosis of the liver the induration and loss of expansibility caused by the new connective tissue are not so great as they would be were the new tissue not composed largely of elastic fibres. In cicatricial contractions, especially in the myocardium, the new tissue contains many elastic fibres to diminish the evil effects of the contraction. In chronic passive congestion when the organ must force on a large volume of venous blood, we find the new tissue very rich in elastic fibres. On the other hand when there is no need for elasticity, the new tissue consists simply of the white fibrous variety, as in the thickened capsule of chronic perisplenitis and in the sclerotic patches in serous membranes. In almost all cases he finds these fibres derived from the adventitia of the blood-vessels; the fibres grow slowly and are very resistant to degenerative changes.

⁶ *Centralbl. f. path. Anat.*, 1897, viii, p. 849.

⁷ *Ziegler's Beiträge*, 1899, xxvi, p. 546.

The formation of elastic fibres being thus always compensatory, always for a definite purpose, Melnikow-Raswedenkow thinks there is no reason why they should share in the formation of new growths which are entirely harmful in character; and as a matter of fact, he finds that they do not play any part in such growths. He does not enter into the subject in detail, but states that he has formed this conclusion from the study of many cases of benign and malignant neoplasms; and mentions adenofibroma, fibromyoma, sarcoma, carcinoma simplex and scirrhus, and cystoma glandulare. He thinks that the frequent occurrence of degenerative changes in the centre of new growths is due to this lack of elastic fibres in their stroma and the consequent imperfect circulation.

In the discussion following Ziegler's presentation of Melnikow-Raswedenkow's investigations before the Deutsche pathologische Gesellschaft⁸ his results met general confirmation, but Hansemann stated that in a single instance (sarcoma of the lung) out of 150 malignant tumors examined he had found increase of elastic fibres, and Schmorl and Orth added that they had each found elastic fibres in a single tumor, the former in a gastric cancer, and the latter in a cancer of the thoracic duct.

I have been unable to find much that is definite on this subject in the writings of other authors⁹. It would seem at first sight entirely possible that, inasmuch as all forms of connective tissue are found as elements of tumors, this one variety should also be found, either as a minor part of the growth or forming its chief constituent. Also, considering that the stroma of tumors is formed from the stroma of the organ in which the new growth occurs, it would seem quite possible that when this organ is rich in elastic fibres the newly-

⁸ *Verhandl. d. deutschen patholog. Gesellschaft*, 2^{te} Tagung, p. 235, Berlin, 1900.

⁹ After this paper was completed and sent to the editor there have appeared the interesting articles of H. U. Williams, "Concerning the new formation of elastic fibres, especially in the stroma of carcinomata" (*Contributions to the Science of Medicine* dedicated by his pupils to William Henry Welch, p. 291, Baltimore, 1900), and of W. C. White, "The distribution of connective tissue in new growths" (*Bulletin of the Johns Hopkins Hospital*, 1900, xi, p. 185). These articles cannot be considered in this paper.

formed stroma should also contain them, as it contains new blood-vessels.

In investigating this question as to the participation of elastic fibres in the formation of neoplasms I chose the Weigert stain,¹⁰ which gives very excellent results, irrespective of the hardening fluid used. It can be used without counter stain, the blue-black fibres standing out against a light blue or almost colorless background; or, if it is desirable to stain the cells, the counter stain advised by Weigert, lithium-carmin, may be employed. A good contrast is obtained with hæmatoxylin and eosin, but a much more striking one by rapid treatment with Van Gieson's stain and hæmatoxylin. In such sections the cells are stained yellow, nuclei brownish, the white fibrous tissue pink and the elastic fibres blue-black.

As most investigators are agreed that the formation of elastic fibres in hyperplastic connective tissue is a slow process and that the new fibres come from the preexisting ones, I looked for the best results in benign connective-tissue growths occurring in tissues normally rich in such fibres, and therefore selected first for examination fibromata of the subcutaneous tissue. The result in most cases was disappointing. Elastic fibres were present in narrow strands between bundles of white fibres, but in such small numbers that it was impossible to be sure that they were not the preexisting fibres of the subcutaneous tissue which had been pushed apart by the new growth. In only one case were the fibres more numerous, irregularly scattered in thick twisted bundles. This same appearance was found in a myo-fibroma of the uterus. Better results were gained from adeno-fibroma and pericanalicular fibroma of the mammary gland where the proliferation of elastic fibres was often quite extensive. In the normal mammary gland elastic fibres of moderate thickness are found forming bands around the excretory ducts, while a few very delicate ones may be seen in the stroma between the lobules. In the above-named neoplasms these bands around the ducts are often increased in thickness and fibres can be seen running out into the surrounding tissue, while thick bundles of fibres are found in the interacinous stroma

¹⁰ *Centralbl. f. allg. Path. u. path. Anat.*, 1898, ix, p. 289.

as well as in the stroma between the lobules. The elastic tissue of the adventitia of the blood-vessels is increased and sometimes the fibres pass out into the surrounding tissue. In none of these cases, however, did the elastic fibres form a conspicuous element of the tissue, and in some they were very scanty in number. No tumor of this class was found which consisted of elastic fibres exclusively.

Turning then to the question of their presence in the stroma of malignant tumors I chose as the most promising the scirrhus carcinomata. The tumors examined were from the pancreas, mammary gland and liver. The distribution of elastic fibres in the normal pancreas is similar to that in the mammary gland, namely, in slender bands around the excretory ducts, a few delicate fibres in the interlobular tissue, and of course in the walls of the blood-vessels. The liver is much more abundantly supplied with these fibres, which are present in such large numbers in the interlobular connective tissue that they seem to leave little room for any other sort of tissue. Almost all of the scirrhus carcinomata from these organs which were examined for this purpose were found to contain large numbers of elastic fibres far more than had been found in any of the fibromata examined. The fibres in some cases seemed to come from the preexisting ones around the ducts or vessels, but were far more abundant than in normal tissue and passed from these regions to the surrounding stroma. This was especially true of the two cases of scirrhus of the liver, originating in the bile-duct epithelium. Not only the stroma of the new growth but the hyperplastic connective tissue throughout the organ consisted largely of elastic fibres which radiated from the adventitia of the blood-vessels and bile-ducts. In scirrhus of the pancreas the elastic fibres were not so numerous and were found in thick masses scattered irregularly in the stroma of white fibrous tissue. Two cases of scirrhus of the liver and one of the pancreas showed a peculiar arrangement of these fibres. They formed a series of quite well-marked concentric rings around a centre which was made up of carcinomatous cells in nests lying in a stroma quite free from elastic fibres (Plate VIII, Fig. 1). This appearance might be explained by the more rapid growth of this portion of the tumor, which had pushed

aside the elastic fibres of the more fully-developed stroma. Such an arrangement does not show at all in sections stained by the usual methods.

In scirrhus of the mammary gland the elastic fibres were found around the excretory ducts, around the nests of cancer cells and in the interlobular connective tissue. In some, these fibres were delicate, wavy, arranged in regular bands; in others, thick, short, twisted, arranged in heavy masses. Always the appearance was characteristic of elastic fibres—the variable thickness of the fibres, the wavy outline and curled ends. Usually they occurred in scattered groups, but occasionally they were woven in with the stroma quite evenly. In almost every case they formed a conspicuous element in the new growth.

Contrary to expectation, it was in the soft, malignant tumors of epithelial origin, where the connective-tissue stroma was delicate and there was every evidence of rapid development, that the richest growth of elastic fibres was found. In adeno-carcinoma of the uterus (Plate IX, Fig. 3), stomach and mammary gland (Plate VIII, Fig. 2), the stroma in many instances consisted largely of elastic fibres, and very seldom were they altogether wanting. In several cases these fibres were found only in the thicker trabeculæ of the stroma, and in two instances the deeper part only of the tumor contained them, the fibres ceasing gradually as the margin of the growth was approached.

The only forms of sarcoma which promise success in such an examination are fibro-sarcoma and alveolar sarcoma, and good results were obtained in examples of both these groups. A melanotic alveolar sarcoma showed thick, twisted bands of elastic fibres in the stroma; a fibro-sarcoma showed delicate wavy fibres passing between the cells. In neither of these two was there any apparent connection between these fibres and those in the adventitia of the blood-vessels, but in a fibro-sarcoma of the brain this connection could be plainly seen. This tumor, which I have described in this Journal,¹¹ evidently originated in the outer walls of the blood-vessels and possessed a stroma made up entirely of elastic fibres, which ran in bands, radiating from the ves-

¹¹ *Journal of Experimental Medicine*, 1899, iv, p. 597.

sels, or were collected in rosettes. In this case all of the fibres were elastic, in the other two the background for these fibres was made up of slender bands of white fibrous tissue (Plate IX, Fig. 4).

It may be objected that the elastic fibres found in these tumors are simply those which were already present in the tissue in which the growth occurs. In answer to this, several arguments may be advanced to prove that there is in the cases described a formation of new fibres, which is sometimes very extensive. In the first place they are found in tumor masses where there is no question that we have to do with a newly-formed stroma, not an infiltration of the original tissues. In the second place they are found in numbers far greater than those normally present in the organ affected. Thirdly, they are found in scattered masses not in connection with vessels or ducts, although normally the organ in question contains elastic fibres only around the excretory ducts and blood-vessels. Thus in the scirrhus of the pancreas represented in Plate VIII, Fig. 1, the elastic fibres are abnormal in quantity and arrangement. Indeed the number found in the tumor often bears no relation to that normally present in the tissue in which the growth occurs. Several specimens of carcinoma of the uterus contained a stroma very rich in such fibres, while two examples of carcinoma of the lung and several of carcinoma in subcutaneous tissue contained none at all. In scirrhus of the liver different parts of the same tumor show different numbers of these fibres and their arrangement is very often, as in the pancreatic and mammary tumors, entirely different from that in the normal organs.

The term "proliferation" as applied to elastic tissue is, of course, rather loosely employed. Strictly speaking "formation" or "deposition" would be more accurate, though an exact term cannot be found until the nature of the process is better understood. The dispute between histologists as to the cellular or intercellular origin of these fibres is still maintained, and the same lack of agreement is found among those who have studied their formation under pathological conditions. Langhans and Dmitrieff from their studies of arteriosclerosis conclude that the fibres originate in the intercellular matrix, while Heubner and Jores, working upon the same sort of tis-

sue, decide in favor of their cellular origin. It is impossible for me to speak decidedly on this point from my observations of new growths, but it is certainly true in my experience that the tumors containing the largest numbers of elastic fibres are those which possessed a stroma comparatively rich in connective-tissue cells, which would seem to indicate that the cells play an important part in the formation of these fibres.

DESCRIPTION OF PLATES VIII AND IX.

PLATE VIII.

Fig. 1.—Scirrhus carcinoma of the pancreas, showing elastic fibres arranged in rings around a central area. Weigert's stain—counterstained with lithium carmine. Leitz, Obj. 3; Oc. 3.

Fig. 2.—Alveolar carcinoma of the mammary gland. Weigert's stain—counterstained by Van Gieson's method. Leitz, Obj. 6; Oc. 3.

PLATE IX.

Fig. 3.—Alveolar carcinoma of the uterus. Weigert's stain—counterstained with lithium carmine. Leitz, Obj. 6; Oc. 3.

Fig. 4.—Fibro-sarcoma. Weigert's stain—counterstained by Van Gieson's method. Leitz, Obj. 3; Oc. 3.

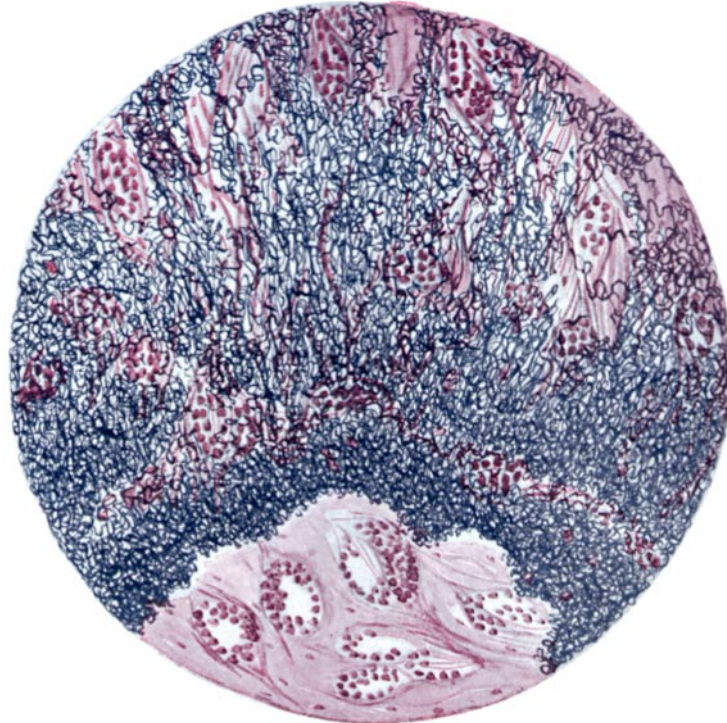


FIG. 1.

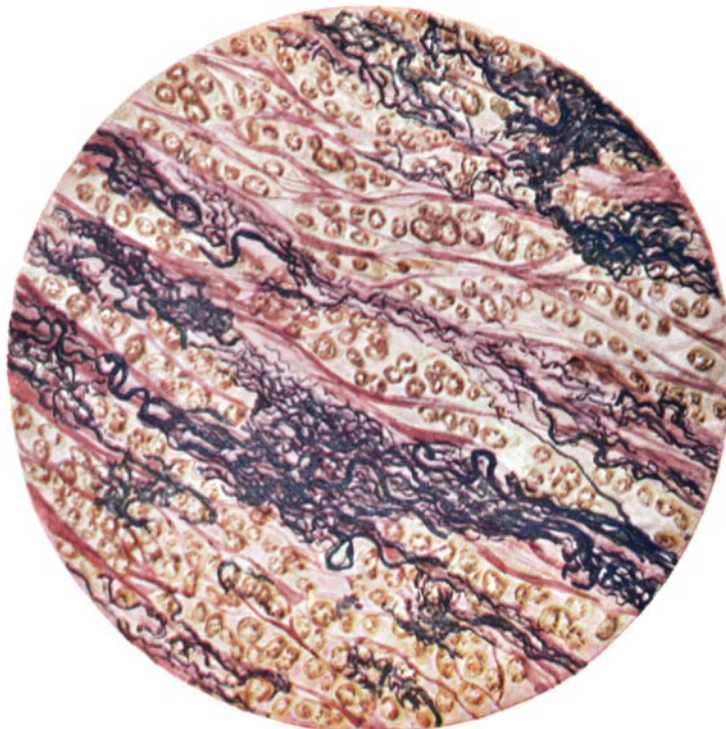


FIG. 2.

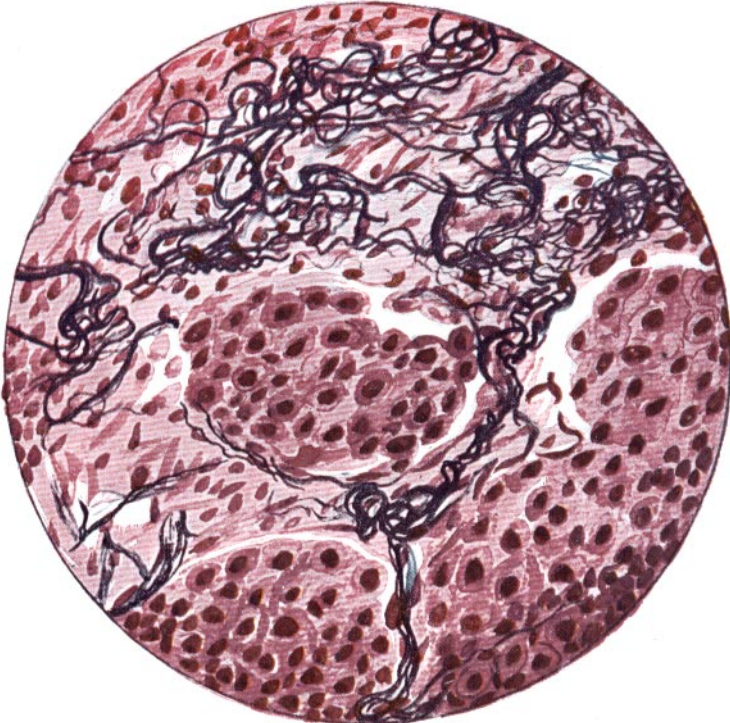


FIG. 3.



FIG. 4.