#6. DYNAMICS OF MORPHOLOGICAL CHANGES IN THE CONNECTIVE TISSUE CAPSULES WHICH DEVELOP AROUND PLASTIC IMPLANTS IN THE PROCESS OF MALIGNIZATION

A. Kh. Kogan and N. T. Raykhlin (Moscow)
The Department of Pathological Physiology (Chief - Professor S. M. Pavlenko) of the I. M. Sechenov First Moscow Order of Lenin Medical Institute (Director - Corresponding Member of the Academy of Medical Sciences, USSR, Professor V. V. Kovanov) and the Laboratory of Pathological Morphology (Chief - Assistant Professor I. A. Avdeyeva) of the Institute of Experimental and Clinical Oncology of the Academy of Medical Sciences of the USSR (Director - Active Member of the Academy of Medical Sciences USSR, Professor N. N. Blokhin).

Translation of: "Dinamika Morfologicheskikh Izmeneniy Soyedinitel'-notkannykh Kapsul, Razvivayushchikhsya Vokrug Plastmassovykh Implantatov, v Protsesse Malignizatsii," Arkh. Pathol., 23, (12), pp. 62-68, 1961

#6

DYNAMICS OF MORPHOLOGICAL CHANGES IN THE CONNECTIVE TISSUE CAPSULES WHICH DEVELOP AROUND PLASTIC IMPLANTS IN THE PROCESS OF MALIGNIZATION[1]

A. Kh. Kogan and N. T. Raykhlin (Moscow)
The Department of Pathological Physiology (Chief - Professor S. M. Pavlenko) of the I. M. Sechenov First Moscow Order of Lenin Medical Institute (Director - Corresponding Member of the Academy of Medical Sciences, USSR, Professor V. V. Kovanov) and the Laboratory of Pathological Morphology (Chief - Assistant Professor I. A. Avdeyeva) of the Institute of Experimental and Clinical Oncology of the Academy of Medical Sciences of the USSR (Director - Active Member of the Academy of Medical Sciences USSR, Professor N. N. Blokhin).
Translation of: "Dinamika Morfologicheskikh Izmeneniy Soyedinitel'notkannykh Kapsul, Razvivayushchikhsya Vokrug Plastmassovykh Implantatov, v Protsesse Malignizatsii," Arkh. Pathol., 23, (12), pp. 62-68, 1961.

At the present time the blastomogenic effect of a number of plastics has been shown, cellophane, polyvinyl chloride, polyethylene, polystyrene, nylon, perlon, dacron, ivalon, etc. [21-25, 26, 16, 3-12, 17-20, 2, 13, 15].

The blastomogenic effect of plastic is pronounced in varying degrees depending on the form, size, and other properties of the implanted material. However the dynamics of morphological changes of connective tissue during its development surrounding the implanted plastics and the principles of its malignization have been inadequately studied. In the literature there are only scattered studies on this question [25, 17, 2, 13, 1, 15].

According to the data of these investigations, over the course of a latent period which extends for a minimum of 6 months, the formation and maturation of the connective tissue capsule surrounding the implant occurs. According to Oppenheimer, by the end of the latent period (after 6 months or more), among the tissue structures of the capsule wall isolated foci of proliferation appear which subsequently change into sarcomatous centers.

The task of this study was an experimental study of the morphological changes of connective tissue capsules which develop during the implantation of plastics, and in the process of its malignization.

---

[1]This study, together with the results of a histochemical investigation, was reported at a conference on the histochemistry of polysaccharides 5-7/V 1960, in Moscow (see Voprosy Onkologii, 1961, No. 9, pp. 13).

Material and Method

Two series of experiments were set up using albino mongrel male rats weighing from 150 to 200 grams. In the first series of experiments, a compression capsule made of sheets of polyvinyl chloride was placed around a kidney in 80 of the animals according to a method described earlier. In the second series of experiments, finely cut up bits of plastic made from sheets of polyvinyl chloride and cellophane [8] were implanted near the kidney in 52 rats. The rats were killed after implantation on the 3rd, 10th, 15th, 30th, 90th, 195th, 285th, 300th and 380th day. Bits of tissue were fixed in Karnua fluid and were poured onto paraffin. The slides were stained with Hematoxylin-eosin, picrofucsin after van Hyson, and were impregnated after Homory.

The first series of experiments. The formation of the connective tissue capsules surrounding the implant begins with aseptic inflamation in the form of hyperemia, disorders of vascular permeability, and infiltration of the surrounding tissue by lymphoid cells and leucocytes. Proliferative phenomena very rapidly begin to predominate. As early as the 3rd day, one can observe an intensive increase of proliferation of immature fibroblasts surrounding the implant and the appearance of fine argyrophil fibers.

On the 10th to 15th day the capsule has already formed, is rich in fibroblasts, and consists of collagen fibers (Figure 1), intensively stained with picrofucsin in red light; in it one can see the newly formed blood vessels with a tender endothelium and a broad lumen filled with blood.

By the 30th day, the capsule consists of thick collagen fibers which have undergone hyalinosis; in places they are arrayed in a certain order or in a disorderly fashion. The number of connective tissue cells in the capsule sharply decreases, one primarily sees mature fibroblasts, which in some regions of the capsule are extended along the collagen fibers and in others are arrayed without any order at all. In certain areas, mainly where the capsule has formed flexures, pouches and pockets, one observes infiltrates of lymphoid cells and scattered leucocytes, as well as small accumulations of connective tissue cells. The number of blood vessels is decreased.

After three months, the capsule contains almost no cells among the dense hyalinized connective tissue; one can detect accumulations of immature and mature fibroblasts which have been scattered over various regions, as well as small cells with circular hyperchromic nuclei (Figure 2). Upon impregnation after Homory, a thick network of argyrophil fibers are revealed between the cells. The blood vessels in the capsule in this period are few; the blood vessels which have been preserved have thickened sclerotic walls and contracted lumina.

Figure 1. A Formed Connective Tissue Capsule on 15th Day. One can see the collagen fibers, the infiltration by lymphoid and connective tissue cells; in the capsule there are newly formed blood vessels (stain - Hematoxylin-eosin X130).

Figure 2. Formation In a Sclerotic Capsule (after 3 months) of Dispersed Accumulations of Connective Tissue Cells (stain Hematoxylin-eosin. X270).

After 6.5 months the capsule preserves its ununiform structure of dense hyalinized connective tissue and almost throughout it is poor in cellular elements, having scattered blood vessels, with thickened sclerotic walls and contracted lumina. The collagen fibers are thick and are located in the form of [TR note: words missing - not copied] bundles, which are extended along the capsule [TR note: more missing words] during impregnation they yield a bluish-brown color. In certain places in the midst of the field of dense hyalinized tissue, basically having a nonhomogeneous structure, one can see accumulations of fibroblasts, while in a number of cases there are large focal growths (Figure 3) of polymorphic connective tissue cells with a scatter of massed cells and a small number of small circular cells with hyperchromic nuclei (Figure 4). In these places the

collagen fibers run in different directions and have varying thickness and length. Upon silvering, a fine network of argyrophilic fibers is revealed between the polymorphous cells. Such focal proliferates are seldom located in the outside layer of the connective tissue capsule; occasionally they are quite clearly delineated from the surrounding tissue, sometimes toward the periphry-the number of cells gradually decreases. The blood vessels in the tissue surrounding the focal proliferation are seldom encountered, while in the proliferate they are more frequently encountered but here they have either a thickened sclerotic wall (Figure 5), or they are reduced in size. During the macroscopic investigation the focal proliferates are reminescent of white plaque or nodules located on the even surface of the capsule.

Figure 3. Focal Proliferation After 6.5 Months (presarcoma) (stain - hematoxylin-eosin. X130).

Figure 4. Focal Proliferation Consisting of Polymorphous Connective Tissue Cells and Small Cells with Circular Hyperchromic Nuclei (stain - Hematoxylin-eosin. X500).

After 9.5 to 12.5 months, in certain preparations one can see a fine sharply hyalinized thickened connective tissue capsule with scattered fibrocytes in the field of vision with white blood vessels. The capsule consists, as a rule, of thick bundles of collagen fibers which yield a violet-brown shade upon impregnation. In certain cases one notes changes in the capsule which correspond to the changes encountered after 6.5 months and which are described above. In 6 of the 16 rats which lived 9.5 to 12.5 months, the development of sarcoma was observed.

Macroscopically, the sarcoma took the form of nodules having incorrect shape ranging in size from 1X2 to 5X10 cm and was pale in color. The tumor doubled in size and invaded the adjacent organs, including the kidney, which proved to be involved with the tumor (Figure 6). Frequently one could see regions of necrosis in the tumor sections. Microscopically, the tumor consisted of atypical sharply polymorphic, occasionally distended connective tissue cells with collagen fibers of differeing lengths and thicknesses running in different directions (Figure 7). With respect to its structure, the tumors could be included among the polymorphocellular sarcomas and fibrosarcomas. The tumors invaded the cellular material and did not invade the noncellular filtrates.

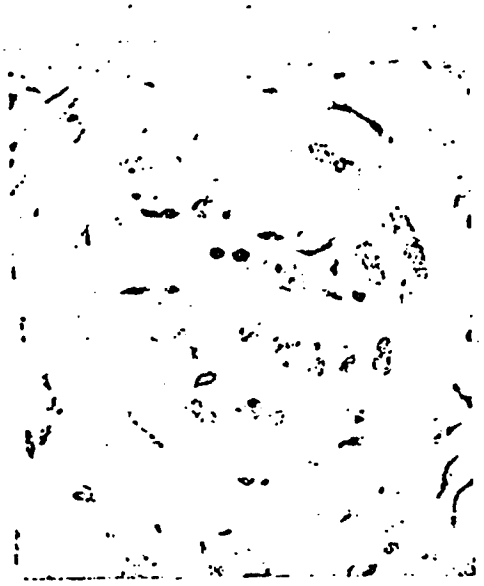

Figure 5. Sclerotic Blood Vessel With a Contracted Lumen in the Region of Focal Proliferate (stain - hematoxylin-eosin. X500).

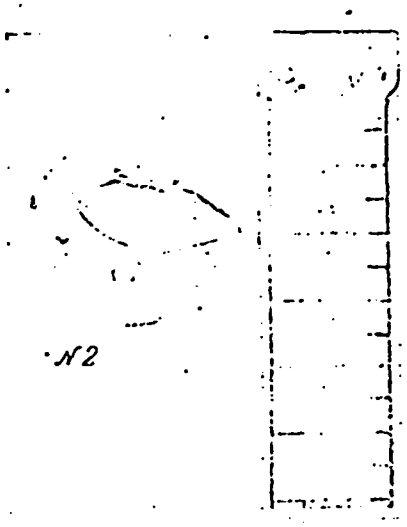

Figure 6. Formation of Tumorous Regions in the Capsule Invading the Kidney.

The second series of experiments. The appearance of the connective tissue capsule surrounding the granulated polyvinyl chloride and cellophane (finely cut bits of plastic sheeting) also began with the development of aseptic inflamation with a predominance of proliferative phenomenon. By the 10th to 15th day the capsule forms with multiple interlocking cross areas of different size and thicknesses surrounding the individual fine bits of sheet. The connective tissue consists of collagen fibers of varying thickness and a large number of immature and mature fibroblasts as well as lymphoid cells. After 30 days the number of cellular elements in the capsule sharply decreases. The collagen fibers thicken and hyalinized;

however in certain cases, in places, one can observe diffuse accumulations of lymphoid cells and scattered leucocytes. By the 3rd month the capsules surrounding the small bits of polyvinyl chloride and cellophane consist of fused thick collagen fibers, hyalinized to a significant degree, with individual fibroblasts and fibrocytes. Occasionally the groups of mature fibroblasts are located with the inner edge along the bits of plastic, and in a number of cases in the center of the capsule one can see connective tissue proliferates. In the formed connective tissue there are few blood vessels.

At 6.5 months the connective tissue cross elements of the capsule are a dense hyalinized tissue poor in blood vessels. There are few cells and only in certain regions can one see small groups of fibroblasts.

After 8 months, in part of the cases, the connective tissue capsules were fine and dense and consisted of thick collagen bundles with pronounced hyalinosis; there were very few cells: in the field of vision one could only see scattered fibrocytes. The few blood vessels which remained were sclerotic and their lumina were contracted. In certain observations, against a background of hyalinized capsule, in certain regions small accumulations of connective tissue cells were detected.

After 12.5 months the connective tissue capsules had a structure similar to the capsules described at 8 months.

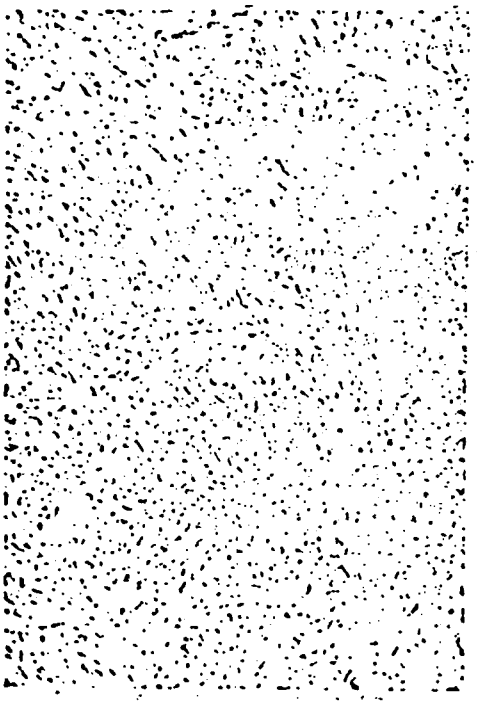

Figure 7. The Development of a tumor of the Fibrosarcoma Type in a Connective Tissue Capsule After 9.5 Months (stain - Hematoxylin-eosin, X130).

L. M. Shabad [14] distinguishes four basic stages in the development of malignant tumors: 1) diffuse hyperplasia; 2) focal hyperplasia; 3) benign tumor and 4) malignant tumor. The development of the tumor can stop at any stage. Moreover, certain stages emerge from blastomogenesis, in connection with which there is a change in the sequence of stages. Thus, for example, focal hyperplasia can directly become the source of a malignant tumor.

During an examination of the data obtained by us with respect to the appearance of sarcoma in the animals during implantation of polyvinyl chloride in them one can note that they basically correspond to the principles reflected by L. M. Shabad in the classification of stages of tumor development [14].

The first stage of development of connective tissue surrounding the implant is characterized by the formation of granulated tissue which in certain regions develops by the 10th to the 15th day and in others by the 30th day and which enables the formation of a dense, hyalinized capsule poor in cells and blood vessels.

In part of the observations with implantation of a compressed capsule and in an overwhelming majority of the cases with implantation of finely cut sheets, the connective tissue capsules gradually continue to thicken and to hyalinize; they are very poor in cells and blood vessels and in this condition can apparently exist until the end of the animal's lifetime without developing into a tumor.

However in part of the cases, in the 3rd month following implantation of the plastic sheet, in such a hyalinized dense capsule and in various of its regions one can see certain small groups of connective tissue cells.

The development of a fine argyrophilic network between cells makes it possible to speak of the formation of proliferates of connective tissue elements. It seems possible to us to characterize the changes as a stage of dispersed proliferates ("hyperplasia" -- second stage in the development of the capsule).

The same groups of connective tissue cells can be found not only during implantation of a compression capsule on the kidney, but also during the implantation near the kidney of finely cut bits of sheeting. The latter in our observations did not lead to the development of a tumor. This fact is in agreement with data of the literature [6-10, 19, 20, 24]. Implantation of cut up cellophane in the kidney, in the presence of a special additional condition -- simultaneous ligature of the urinary duct -- caused the development of carcinoma and a precancerous tumor [12].

The third stage of development and malignization of the capsule -- the formation of focal proliferates of polymorphic cells -- was pronounced quite clearly and was observed by us only during the implantation of the compression polyvinyl chloride capsule (in approximately 1/3 of the animals after 6.5 months or more following implantation).

3. The implantation of chopped plastic bits in rats (polyvinyl chloride and cellophane) near the kidney did not enable the development of tumors.

REFERENCES

1. Васильев Ю. М. J. nat. Cancer Inst., 1959, v. 23, p. 441. — 2. Васильев Ю. М., Ольшевская Л. В., Иванова О. Ю. В кн.: Доклады 1-й конференции по вопросам цито- и гистохимии. М., 1960, стр. 61. — 3. Коган А. Х. Арх. пат., 1952, в. 2, стр. 61. — 4. Коган А. Х., Чечулин А. С., Алиев М. А. Там же, 1955, в. 2, стр. 65. — 5. Коган А. Х., Чечулин А. С. Нат. физиол. и экспер. тер., 1957, № 1, стр. 39. — 6. Коган А. Х., Чечулин А. С. при участии Ведрова Н. Н. и др. Арх. пат., 1958, в. 1, стр. 41. — 7. Коган А. Х. Нат. физиол. и экспер. тер., 1959, № 2, стр. 74. — 8. Он же. Гиг. труда и проф. заболевания, 1959, № 1, стр. 16. — 9. Он же. В кн.: Berliner Symposion über Fragen der Carcinogenese. Abhandlungen. Berlin, 1960, S. 90. — 10. Коган А. Х., Тугаринова В. Н. Вопр. онкол., 1959, № 5, стр. 510. — 11. Коган А. Х., Мардахаишвили Ш. И. Арх. пат., 1961, в. 4, стр. 43. — 12. Коган А. Х. Нат. физиол. и экспер. тер., 1960, № 3, стр. 70. — 13. Ольшевская Л. В. Бюлл. экспер. биол. и мед., 1961, № 3, стр. 116. — 14. Шабад Л. М. Вопр. онкол., 1956, № 1, стр. 10. — 15. Alexander P., Horning E. S. В кн.: Ciba Foundation Symposium on Carcinogenesis. Mechanisms of Action. London, 1959, p. 12. — 16. Druckrey H., Schmahl D., Z. Naturforsch., 1952, Bd 76, S. 353. — 17. Mohr H. J., Nothdurft H., Klin. Wschr., 1958, Bd. 36, S. 493. — 18. Nothdurft H., Naturwissenschaften, 1955, Bd. 42, S. 106. — 19. Idem, Strahlentherapie, 1956, Bd. 100, S. 192. — 20. Idem, В кн.: Berliner Symposion über Fragen der Carcinogenese. Abhandlungen. Berlin, 1960, S. 80. — 21. Oppenheimer B. S., Oppenheimer E. T., Stout A. P., Proc. Soc. exp. Biol. (N. Y.), 1948, v. 67, p. 33. — 22. Idem, Ibid., 1952, v. 79, p. 366. — 23. Oppenheimer B. S., Oppenheimer E. T., Stout A. P. et al., Science, 1953, v. 118, p. 305. — 24. Oppenheimer B. S., Oppenheimer E. T., Danishefski I. et al., Cancer Res., 1955, v. 15, p. 333. — 25. Oppenheimer B. S., Oppenheimer E. T., Stout A. P. et al., Cancer, 1958, v. 11, p. 204. — 26. Zollinger H. U., Schweiz. Z. allg. Path., 1952, Bd. 15, S. 666.