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AMYLOIDOSIS IN MALIGNANT TUMORS*

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The denomination of diseases involving a formation and deposition of the substance known as amyloid, is as yet not very definite in the medical science. Determinations like primary, secondary, typical, atypic, tumorlike, local, general amyloidosis, or the term paramyloid, are covering ideas of a vague character. It would appear most to the point to classify the cases as primary and secondary amyloidosis. Cases where the cause of the deposition is recognisable (tuberculosis, syphilis, chronic abscess, necrotic tumor, lymphogranulomatosis, etc.) can be called *secondary*, while a *primary* case may be spoken of, if none of the mentioned causes of amyloid deposition can be traced. In the latter cases the amyloid depositions usually do not occur in the customary places, but for instance in the striated musculature, the tongue, the urinary bladder, etc. Such cases *are termed paramyloidosis* by many authors and the *local* and *experimental* amyloidosis, too, can be regarded as belonging to this group. It is typical for paramyloid, that it very irregularly gives the histochemical reactions characteristic for ordinary, i. e. secondary amyloid.

The cases we propose to deal with refer to local amyloidosis. Amyloid depositions were found in malignant tumors or in their immediate neighbourhood. Biopsy was made in the case of each patient, consequently the tumors were comparatively fresh. Not one of the patients suffered from cachexia and their complaints were only based on local symptoms of tumor. General amyloidosis examinations gave a negative result in each ease.

1. The *first case* is a *parotistumor* which histologically proved to be a malignant salivary glandular adenoma. In the abundant stroma of the tumor, amorph masses are recognizable showing a vivid red colour when dyed with eosin, which from here penetrated the lobuli, where the thinner bundles enclose 6 to 8 tumor cells. In some places these cells became atrophied and the picture resembles to that of liver amyloid to be seen in text-books. The homogenous, extraneous substance turns yellow by van Gieson and metachromatic lilac red by methyl violet. The picture becomes particularly well freaked with Bismarck brown. Congo red

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dyes it intensively, polychrome methylene blue hardly at all, while iodine-green produces a large scale of shades from achromatic over grey red, up to violet red, according to the different degrees of maturity. When dyed with lugol, the substance obtains but a yellowish shade, after preliminary aluminoferric treatment it turns pale brown. An after-treatment with sulphuric acid results in deepening of the brown colour.

2. The *second case* is a *urinary papilloma.* In the peduncle of the tumor, besides some muscular tissue, there appears a capillary in the wall of which and

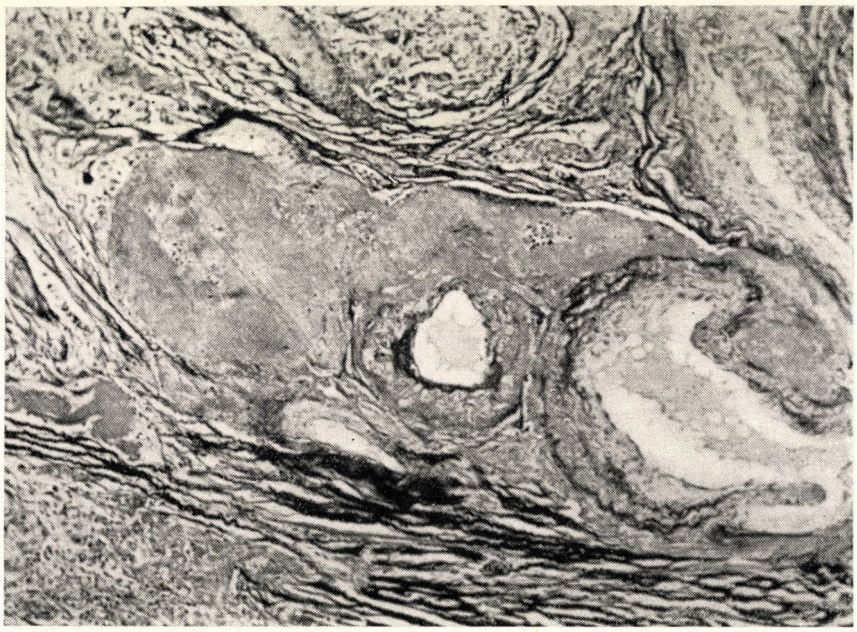

Fig. 1. Amyloid in the capillary wall of a mammary tumor and in the surrounding connective tissue (dyed with van Gieson).

of its immediate vicinity the above described homogenous substance can be observed in larger masses. In the tumor itself nothing of the substance can be traced. The Congo red preparations show the beginning of depositions of the dyed substance in the wall adventitia of the blood vessels; later on the entire wall of the vessel became homogenized. In this case lugol and iodine-green gave a negative reaction, methyl violet colouring resulted in a minimal metachromasia, while positive reaction was attainable with polychrome methylene blue.

3. The same type of alteration has been observed in *13 cases of mammary tumors*, all of which proved to be fibrous carcinoma. (Fig. 1.) Depositions firstly appear in the walls of capillaries and small ducts. They gradually increase to a degree at which these structures were no longer recognizable. Big, structureless homogenous masses are visible in the surrounding connective tissue, too,

which give a vivid red when dyed with eosin, and a yellowish red colour with van Gieson. In the centre of such nodules at places even residues of cancer cells can be found. (Fig. 2.) With Congo red all thirteen have shown an intensive coloration, with iodine-green none, three reacted on polychrome methylene blue, four on methyl violet. Lugol reaction resembled the one of the parotis-tumor, particularly after aluminoferric treatment.

4. Out of six cases of *epithelial carcinoma*, four originated in the lips, two in the *cervix uteri*. The homogeneous masses are still found in the papillary

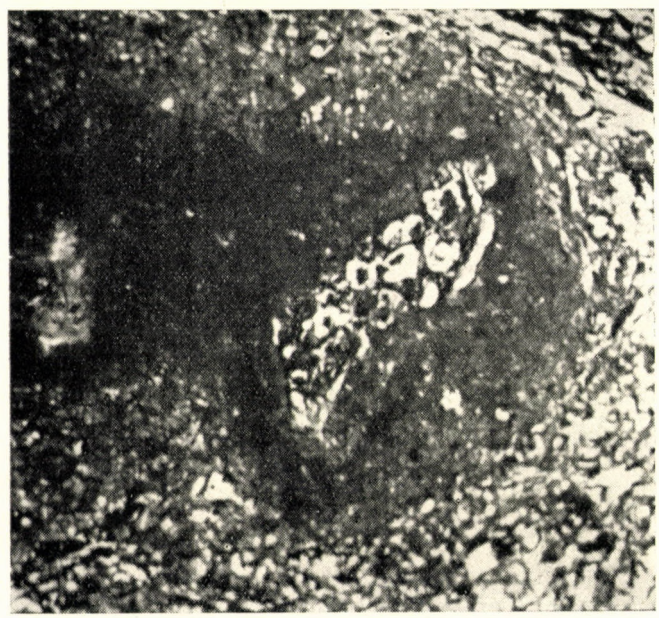

Fig. 2. Cell residues of mammary tumor in a mass of amyloid (dyed with Congo red).

bodies, under the epithelium in the immediate surrounding of the tumor groups. Here the structure is not as homogeneous as in the formerly described cases, nor is it bound to the wall of the blood vessel. It can rather be compared with edematous, homogenized collagen bundles which, however, refuse to receive van Gieson fuchsin. (Fig. 3.) In the cervixcarcinoma the congo-positive homogeneous masses are situated around the capillaries and in the inflamed infiltered connective tissue between the tumor groups. Besides Congo red, methylviolet and polychrome methyleneblue also gave a decided positive reaction while lugol gave a negative one. Indication of iodine-green was observed only in one of the cases.

In biopsies of tumors, where parts of the environments were also included, the circumjacent infiltered inflammation was found to contain, in addition to the lymphocytes and eosinophil cells, a great number of *plasma cells. In the*

interior of some specially large plasma cells inclusions can sometimes be observed showing a brownish reaction when dyed with Congo red.

On the basis of the described morphological and dyeing examinations, the substance in question must be considered as amyloid ; on basis of its clinical and histological behaviour it must be regarded as *primary* or *paramyloid.*

Observations proved that the dyeing reactions of amyloid showed very irregularly. Congo red gave the most constant reaction. None of the customary

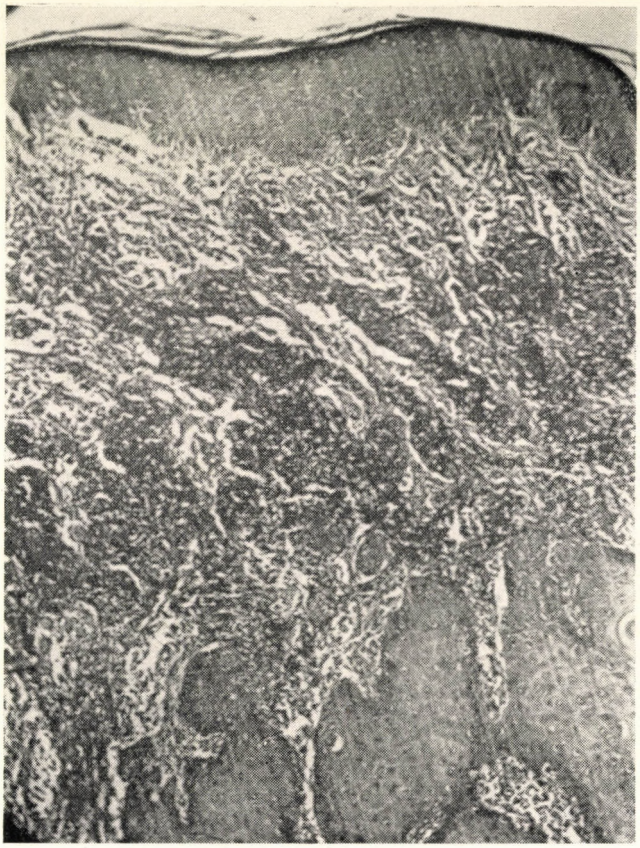

Fig. 3. Amyloid precipitation between the skin epithelium and epithelium cancer (dyed with Congo red).

causes of amyloidosis could be observed on the patients and in these cases the processes were also clinically of a local nature.

The role played by the plasma cells, also shown in our sections, has engaged the attention of a great number of authors *(Björneboe* [5, 6] *and collaborators, Brass* [4], *v. d. Berghe* [3], *Abrikosoff* [1], *Albachary* [2], *Marchal and Mallet* [18], *Dubois-Ferrière* [9], *Schönholzer* [23], *Strauss and Hammer* [24], *Ran-*

ström [19], *Hübschmann* [13], *Bing and Plum* [7], *Bing-Fagreus-Thorell* [8], *etc.).* The majority of authors agree in presuming that these cells have an active part in the production of blood protein, chiefly of protein categories more roughly dispersed, such as globulins and the fibrinogen. In their environment hyperglobulinosis may present itself and the gamma group of the globulins includes the antibodies which appear in the course of immune reactions. The amyloid — as known — has for some time been considered as a substance originating in the course of antigen-antibody-reactions. (Thus by *Letterer* [14, 15], *Löschke* [16], *Schneider* [21], further by *Glebova* [11] and also by *Gindin* [12], v). In the case of

Fig. 4. Small tonsil artery of periarteriitis nodosa (with amyloid in its wall, yellow with van Gieson dyeing).

genuine, so called secondary amyloidosis, the substance appears in the spot of antibody formation (spleen, liver) while in the case of paramyloidosis it gets deposited in a convenient electrocolloidal milieu in the spot of antigen production (f. i. striated musculature, heart), as a rule together with multiplication of the plasma cells and the globulins.

In our cases the antigen is represented by the tumorous tissue itself and by its destroyed proteins respectively. A decisive proof and confirmation hereto is furnished by the Soviet scientist *Zilber* [26], who by an ingeniuos method showed *human and animal tumors to contain specific antigens.* The antigen properties of destroyed proteins were also affirmed on account of our observations, i. e. the strongest amyloidosis appeared in the case of two mammary tumors treated with pre-operational irradiation. A similar observation is recorded by

Löwenberg [17] and collaborators, too, who after X-ray irradation of a hypophysic tumor found amyloid depositions in the neighbouring brain sections.

According to some authors, the appearance of primary amyloidosis may be regarded as the manifestation of immune-biological reaction of the organism, revealing itself as a histologic symptom of organic self-defence (*Teilum* [25] *Stöger* [22], etc.). Our own examinations have confirmed this opinion.

This self-defending reaction is not of a specific nature, for in addition to malignant tumors, its histologic symptoms can be found also with other conditions, which belong to the class of vascular collagen diseases (*Teilum* [25], *Ritama*

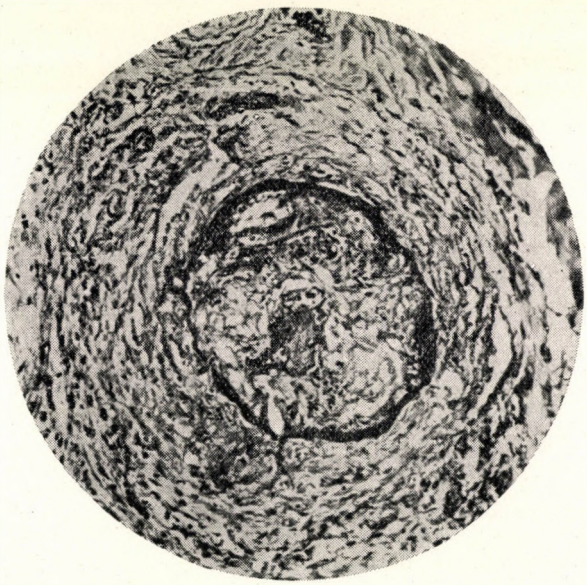

Fig. 5. Boeck sarcoid of the palpebra. Amyloid deposition in circular arrangement (dyed with Congo red).

and Saskela [20]), such as lupus erythematous disseminatus, Letterer-Siwe's disease, scleroderma, etc. The department of morbid anatomy of our hospital registered the appearance of amyloid in the exstirpated tonsil of a patient who suffered from *periarteriitis nodosa* (Fig. 4), further in the *Boeck sarcoid* of the palpebra (Fig. 5) in circular arrangement, resembling the figures of *Teilum* [25]. In these cases the multiplication of plasma cells + hyperglobulinemia + the paramyloid deposition, being histological and clinical symptoms of positive anergia, may be classified as *paramyloid syndrome.*

Summary

Amyloid depositions were observed in malignant neoplasms of the parotid gland, breast, the urinary bladder and the epithelial cancers of the cervix uteri and of the lips. The inflammatory infiltration around the tumors was found to contain a great number of plasma cells. Sometimes inclusions can be observed in them, showing a brownish-red reaction when dyed with Congo red. The plasma cells have an active part in the production of roughly dispersed blood-proteins and hyperglobulinosis may be present in their environments. The appearance of primary amyloid (paramyloid) can be regarded as the manifestation of non specific immune-biological reaction of the organism.

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АМИЛОИДОЗ ПРИ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЯХ

Г. Бернат

Р е з ю м е

Автор наблюдал отложение амилоида при злокачественных опухолях околоушной железы, мочевого пузыря и грудной железы, далее при плоскоклеточном раке губ и шейки матки. Гистохимические реакции, проведенные на этом материале, оказались весьма непостоянного характера (парамилоидоз). Поразительно было то, что в воспалительной инфильтрации можно было наблюдать вокруг опухолей много плазматических клеток. Плазматические клетки активно участвуют в образовании белков более грубой дисперсностью и вокруг последних может образоваться гиперглобулиноз. Группа гамма-глобулинов включает в себе также антитела, возникающие при имунных реакциях. Самым антигеном является опухолевая ткань и белки, возникающие при ее распаде. Образование амилоида можно рассматривать как манифестацию иммунобиологических реакций в организме и как таковую как неспецифический тканевый признак защитной деятельности организма.