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RECENT STUDIES ON THE AMYLOID IN MALIGNANT TUMOURS

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If some antigen enters the organism and conditions are suitable, the organism responds to the antigenic effect by producing antibodies. The own protein of the organism may also assume the role of antigens if they become modified under pathologic conditions. It seems probable that if the amount is small, and the organism is able abundantly to produce antibodies, then the reaction of the antigen with the antibody takes place locally, at the site of origin of the modified protein. If a great amount of antigen is produced, for instance in consequence of tissue destruction, and the organism is not able to respond with the production of an adequate amount of antibodies, then part of the antigen will enter the circulation, or become adsorbed by the reticular system and the reaction will ensue there or in the blood stream *(Loeschke, Lehmann—Facius, Letterer)*. According to *Teilum*, the appearance of a peculiar, homogeneous, hyaline, eosinophilic substance can be observed at the corresponding sites, as a morphological sign of the reaction, particularly under the conditions first described, i. e. in the positive anergic phase of the organism. This eosinophilic substance was found by *Teilum* in cases of lupus vulgaris, Boeck's sarcoid, Letterer—Siwe's disease, lymphogranuloma inguinale, and in acute disseminated lupus erythematodes. According to his examinations, the substance is nearest to hyaline, but it may appear also in transitional forms similar to amyloid. *Haranghy* observed amyloid material in Hodgkin's disease. We ourselves have found in a case of Boeck's sarcoid a precipitate occurring in a peculiar circular arrangement, fully corresponding to the figures of *Teilum*, furthermore also in the small arteries of the removed tonsils of a patient suffering from periarteriitis nodosa. The substance stained intensely with Congo red (Figs. see *G. Bernáth)*.

Since we have found this eosinophilic hyaline substance to occur in several cases of malignant tumours, at our request *G. Bernáth* from our Department of Pathology has studied it and published her results in the Acta Morphologica No. 2. 1952. She observed in the immediate surroundings of cancers of the skin, of the urinary bladder, the breast and the uterine cervix, and in lymphoepithelial tumours, amorphous, homogeneous, esinophilic masses, which stained yellowish-brown with van Gieson and which gave the specific amyloid reactions in a very

unstable manner. In each case the masses stained intensely with Congo red. Most of the cases gave Jürgen's methyl violet reaction. There were, however, some which hardly showed metachromasia, but stained with polychrome methylene blue, or iodine green. When stained with Lugol's solution, the substance turns yellowish-brown, particularly after preliminary treatment with aluminate of iron. Treatment with sulphuric acid results in intensification of the colour. On the basis of the tests described, *Bernáth* has considered the substance in question as paramyloid.

Examinations

We have studied this substance which reacts as amyloid and which since our first observations we have found in a great number of mammary and skin cancers, in adenocarcinoma of the sigmoid, in bronchogenic pulmonary carcinoma and in the more or less malignant adenoma of the parotid gland. Again it was Congo red which proved the most constant from among the usual amyloid stains, giving a positive reaction in each of the tumours examined. Out of the metachromatic stainings usually only 1, or 2, occasionally 3 were successful.

The form in which the substance appears varies and is probably connected with the age of the precipitate. The most mature one is the amorphous form which shows no structure whatever. It is usually found in vascular walls, or in the connective tissue around the vessels, but frequently it is completely independent of them ; in mammary cancers it occurs in the walls of the ducts or simply around the cancerous cell nests. It usually forms large globules, while in other instances it appears surrounding the cell nests in the form of bands or lamellae (Fig. 1). In such a case the cells show marked regressive phenomena. In addition to these principal sites, amyloid deposits may also form smaller nodes, similarly as in the amyloid tumours growing sometimes on the skeleton beside myeloma. We observed such formations, for instance in parotid tumours. Here the structure was slightly concentric, lamellated (Fig. 2). In skin cancers the substance staining with Congo red is often found directly under the epithelium, filling the papillary bodies in the form of broad lamellae.

Around the homogeneous masses fresher stages of the precipitate are usually present. Around the amyloid nodes filamentous structures are frequently visible. The amorphous nodes are surrounded by fragmented, jagged, strongly twisted, wavy fibres or filaments, which often thicken, later break up and form a coarser or finer granulated substance (Fig. 3). This granular substance displays transitional forms to the completely amorphous one. The fibres stain intensely with Congo red and in comparison with the amorphous substance they stain often with methyl violet more intensely. The fibres may also be found at a considerable distance from the homogeneous nodes and also quite independently of the latter in the cancer nests, forming a veritable network of long running, thick, or thin

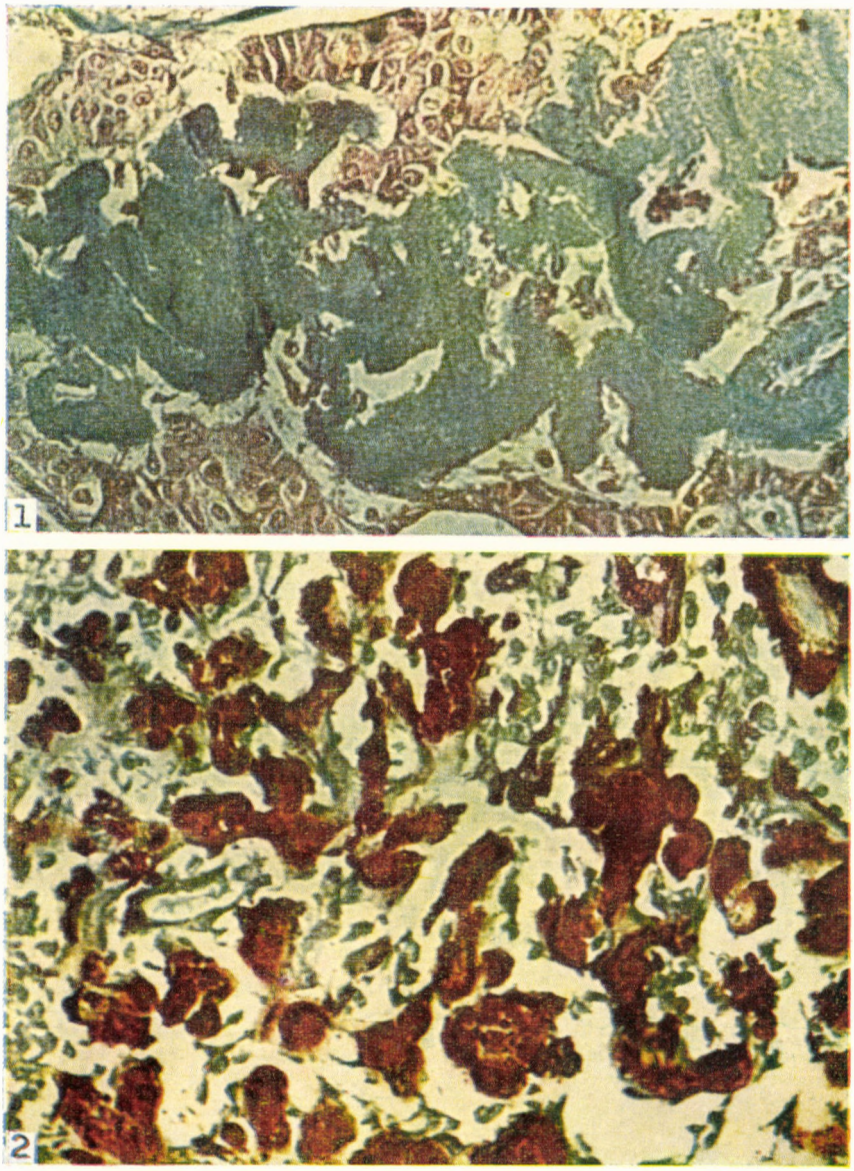
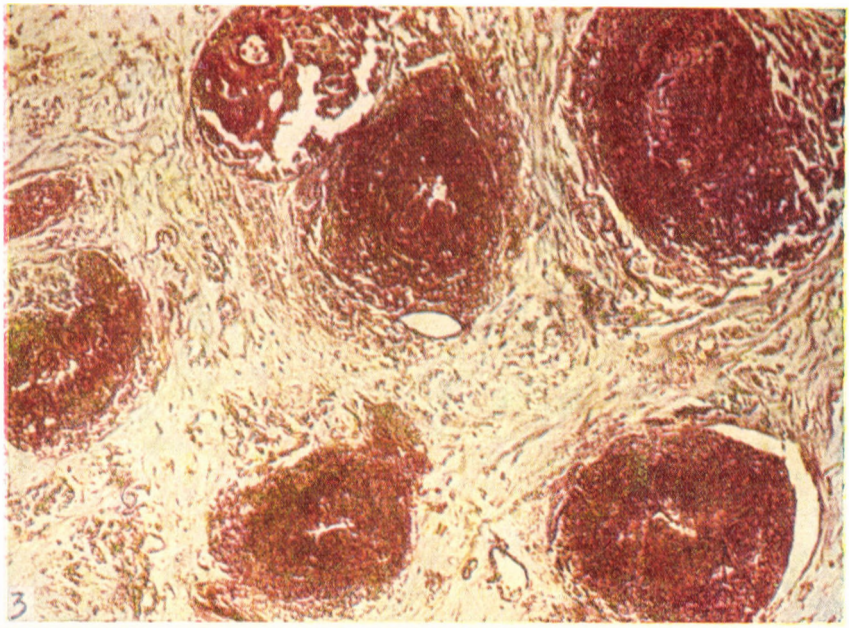


Fig. 1. Mammary cancer. Amyloid in band-like arrangement stained blue by Azan
Fig. 2. Parotid tumour. Amyloid arranged in small nodules. Congo-red. 400 x



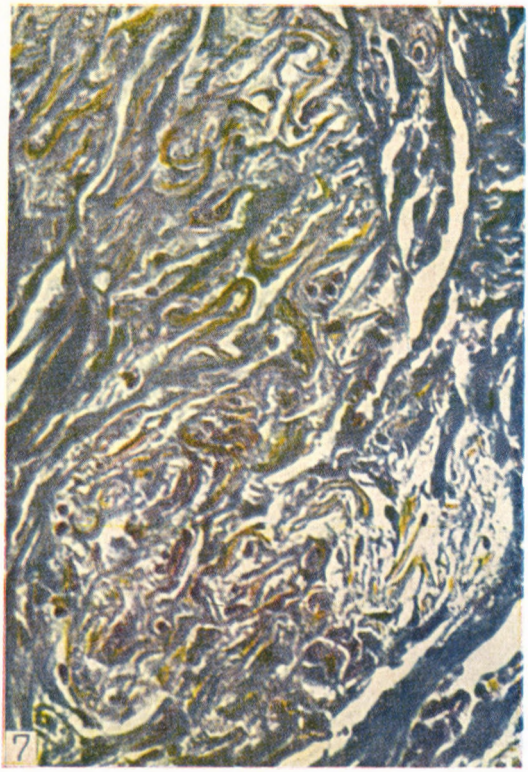


Fig. 3. Mammary cancer. Amyloid deposited in large nodes and filaments. Congo-red. 100 x
Fig. 4. Mammary cancer. The amyloid forms a broad filamentous network. Congo-red. 400 x
Fig. 7. Breast cancer stained with Azan. The filamentous amyloid stains partly blue, partly orange. 400 x

fragmented filaments among the cells (Fig. 4). In some tumours, e. g. in adenocarcinoma of the sigmoid this fibrous substance giving amyloid reactions is the only one to occur around the tumour nests ; the small nodes in parotid tumours are also thrust back by the filamentous-lamellated structures.

As to its morphological appearance, this peculiar, filamentous precipitate giving amyloid reactions shows obviously a great similarity to elastic fibres. It was therefore attempted to apply elastic staining. Much to our surprise this proved positive, insofar as in cases of tumour *the substance staining as amyloid stained without exception intensely with resorcin-fuchsin.* Both the homogeneous masses and the band-like formations in mammary tumours (Fig. 5), and the smaller nodes of the parotid tumour (Fig. 6), as well as the fibrous-filamentous formations stained a dark bluish-violet. The mammary nodes which seemed homogeneous on staining with methyl violet or Congo red, appeared after elastic staining as a tangled mass of a network of elastic fibres merging into the stroma. The amyloid masses found in tumours of the sigmoid, lungs and skin stained with similar intensity. In the latter case the papillary bodies were completely filled with the bluish violet substance which was either homogeneous, or showed a filamentous structure. Amyloid in Boeck's sarcoid also gave a positive reaction.

It was thereafter examined how genuine amyloid behaves on treatment with elastic stain. It was found that neither the nodes in sago spleen nor the amyloid adsorbed to small vessels and to glomerular loops in amyloid nephrosis, or the amyloid tumour occuring on the ribs in a case of myeloma, failed to stain with fuchselin. It was also revealed that neither the paramyloid tumour of the palpebra, nor some so called amyloid tumours of the larynx contained elastic substances.

It was then decided to determine by means of digestion whether the amyloid substance giving staining like elastic material contains genuine elastin. The embedded sections previously thinly coated with celloidin were kept for 1 to 3 hours at 37 °C in a 0,4 per cent solution of the elastase* diluted in a Kolthoff buffer of about pH 10. Subsequently, the sections were stained with resorcin-fuchsin and with Congo red. We observed that the *elastic staining of the amyloid found in tumours disappeared completely after digestion, neither did it stain with Congo red any more.* This equally refers to the homogeneous, as well as the band-like and filamentous forms. Thus after digestion, respectively after dissolution of the elastin, the special staining of the paraprotein adsorbed to elastic masses and giving amyloid reactions has ceased completely. It must be pointed out, that digestion of elastase does not influence either the special staining of organs from cases of generalized amyloidosis, or the capacity of the amyloid tumours of the skin and the larynx, or that of myelomatous cases to stain with Congo red.

*We desire to express our thanks to Mrs. I. Banga for the elastase used in the experiments.

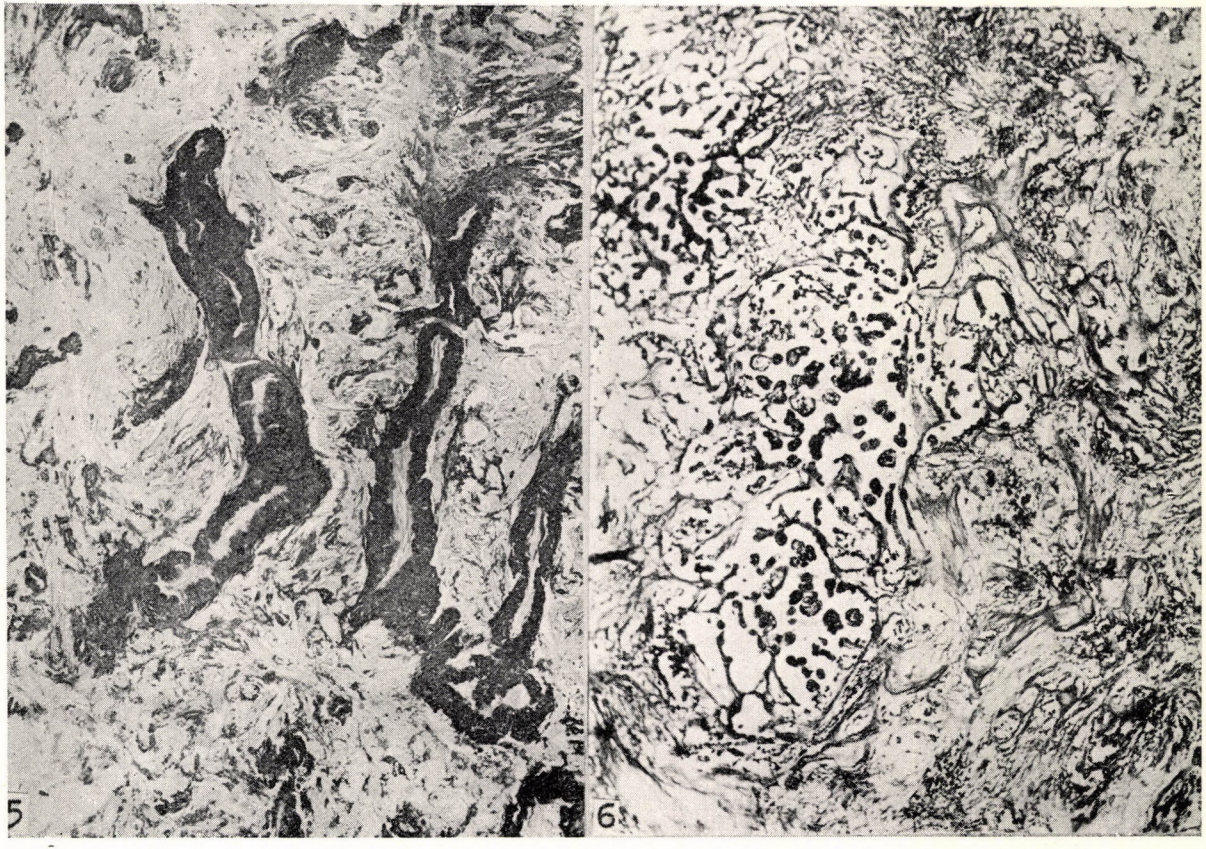


Fig. 5. The mammary tumour of Fig. 1 stained with resorcin fuchsin. 100×
Fig. 6. The parotid tumour of Fig. 2 stained with resorcin fuchsin. 100×

It is generally known that there are two kinds of amyloidoses ; the secondary amyloidosis of known aetiology, (suppurative, tuberculous, etc.) and the primary amyloidosis of unknown aetiology, in which the amyloid deposits do not occur in the organs rich in reticuloendothelial elements, but rather in the heart, in the striated muscles, the tongue, etc. This form of disease has also been termed paramyloidosis *(Picchini* and *Fabris)* and the amyloid tumours of the skin or of the upper respiratory tract are presumably local forms of this disease. Experimental amyloidosis and animal amyloidosis belong also to this group, into which we thought to include also the amyloid observed in tumours. Several authors differentiate also a third group, i. e. the amyloid occuring in cases of myelomatous hyperproteinosis.

Since, according to our experiments, a considerable histochemical difference in elastic staining and in digestibility with elastase manifests itself between the amyloid of generalized amyloidosis as well as of localized amyloid tumours, and the amyloid occurring in malignant tumours and their surroundings, *the inclusion of a fourth group, which should be termed »elastic amyloid« is recommended.*

There are still further histochemical differences to be found between elastic and other amyloids.

1. *Romhányi* demonstrated that the amyloid-Congo red complex displays double refraction. Independently of him, *Ladewig* has confirmed this, pointing out, that the otherwise very weak double refraction of amyloid is considerably augmented after staining with Congo red. This is due to the dichroic stainability of amyloid, which follows from its submicroscopic micellar structure. Our own examinations have confirmed the dichroism described by *Romhányi* in every respect ; common secondary amyloid as well as amyloid tumours of the palpebra or the larynx showed double refraction on staining with Congo red. On the other hand, elastic amyloid displays no double refraction. Thus the paraprotein precipitated in the form of elastic, amyloid does not show a systematic paracrystalline structure. From this it follows that, under certain conditions in tumourous disease, the paraprotein developed locally around the tumour in consequence of an antigen-antibody effect, becomes adsorbed to the probably increased amount of elastic fibres and lamellae present and alters the molecular structure of the protein in such a way, that by taking up side chains it will stain similarly to amyloid. When digested with elastase, the side chains break off, the special staining reactions disappear, but no submiscroscopic micellar-crystalline structure is formed during the time available.*

2. It is known that amyloid takes a sky-blue colour on staining with Azan. There is no difference in this respect between genuine amyloid and the amorphous elastic one. Only in myelomatous tumours and in certain local amyloid tumours was there observed a shade almost reminiscent of the dark blue staining of

* The anamnestic data of the biopsy material obtained had never dated back to more than a few months.

collagen bundles. The filamentous, i. e. less mature form of the elastic amyloid, as well as its granular form, stain, as a rule, a light blue, but occasionally filaments taking a vivid yellow colour occur among the light blue amyloid fibres (Fig. 7). In other cases the filamentous amyloid seen among the dark blue collagen bundles stains red with Azan and settles in large masses around skin tumours. This phenomenon is probably analogous to the »blue,yellow and orange protein« described by *Zakharevskaya*. The same fibres, i. e. those staining light blue, yellow and red, all take the same brownish-red colour with Congo red, blue-red with methylviolet, and black with resorcin-fuchsin. They are digested absolutely alike by elastase. The examination of an amyloid tumour the size of two fists, which occurred on the ribs of the already mentioned patient suffering from multiple myeloma, has called our attention to the similar, non-homogeneous structure of the nodular form of amyloid. On staining with Azan a peculiar, red and dark blue, lamellate, concentric structure appeared in the amyloid nodes. The nodes did not take elastic stains, and displayed slight double refraction when stained with Congo red. A blue and yellow indefinite concentric structure was observed in the nodules of the malignant adenoma of the parotid formerly described ; these nodes, however, stained as elastic material, they were digestible and displayed no double refraction when stained with Congo red.

If we accept that the similar staining properties of amyloid, paramyloid and elastic amyloid are not yet indicative of chemical identity, there is no reason to assume that different staining properties should not indicate a difference in chemical structure *(Leupold)*. It seems probable that differences in the colour taken by amyloid on staining with Azan are due not only to mechanical and physicochemical factors but also to chemical differences in the composition of the proteins adsorbed to the fibres and nodules. In the development, or in the subsequent disappearance of these differences the time factor plays an eminent role.

In the last part of our studies we carried out animal experiments in order to approach the initial phase of the process described. We started from the observations that after X-ray irradiation of pituitary tumours amyloid deposits occur in the neighbouring areas of the brain *(Löwenberg)*, and that after pre-operative irradiation of mammary tumours, unusually large amyloid masses were frequently found. *(Bernáth*'s and *our own* observations.) In animals inoculated with Guérin's tumour, increased destruction of protein could be brought about by repeated X-ray irradiation. Part of the animals died spontaneously after 2 to 3 weeks, the rest was killed after the same time. In the tumours themselves subtances staining with Congo red occurred occasionally, but more frequently in the wall of the vessels within the tumour. The initial process was best seen in those organs in which the subcutaneously inoculated tumour had caused microscopic metastases. Deposits of paraprotein staining with Congo red were found beside these in the walls of the small arteries or in their elastic layer. Amyloid staining was equally intense in organs directly inoculated with the tumour. The amyloid masses

stained with elastic stains. This property and also their staining with Congo red were lost after digestion.

Discussion

On the strength of the above findings we may state that the substance giving amyloid reactions which occurs in tumours and their surroundings, similarly to both the genuine amyloid and the paramyloid of *Picchini* and *Fabris*, has a predilection to the vascular wall, and infiltrates the elastic elements. *(Apitz, Wiener.)* The process starts in the inner elastic layer, spreads from here to the vascular walls und from there to the elastic substance of the surrounding stroma, increased in amount owing to the desmogenous effect of cancer. In the advanced stage, deposits of elastic amyloid occur naturally quite independently of vessels.

Here we must briefly mention the staining with Congo red of elastic substances in general. In the literature there are occasional references to the fact that normal elastic fibres stain with Congo red. *Roussy* and *Apitz* have mentioned this, and also *Roulet* refers to it in his well-known book. With *Matsamura*'s Congo red method, after differentiation with phosphotungstic, elastic fibres assume a violet colour. Congo red is an acid benzidine dye belonging to the diazo group of dyes. It was introduced as a special amyloid dye by *Bennhold* in 1922. At present Congo red is considered the best and most constant indicator of amyloid, persisting after digestion with hydrochloric acid and pepsin, as well as after decomposition and passing through the intestinal tract. *(Missmahl)* Other amyloid stainings disappear or change after digestion. (Amyloid stained with Azan assumes a red colour after digestion with hydrochloric acid and pepsin.) The chromatophoric azo group (—N=N—) of Congo red is bound not only by the side chains of the amyloid, but it also stains eleidin, keratin and the peculiar granular substance present in the parietal cells of the stomach. It also stains part of the chromotropic lipids. According to our studies, it also stains the granules of the eosinophilic white blood cells, but after differentiation the staining disappears. Fibrin and fibrinoid precipitated within necrotic areas also stain with Congo red but the colour disappears during differentiation. As to the staining of elastin, we have observed that the network of elastic fibres in the lungs or the skin always fails to stain with Congo red. The dye, however, frequently stains the walls and the elastic elements of the larger arteries and it is difficult to dissolve it from such vessels. Staining with Congo red must be considered positive only in sections in which the connective tissue has discoloured completely in the course of differentiation. As to the inner elastic layer of arteries corresponding in calibre to the small vessels of the kidney, we have observed that in healthy animals it did not stain with Congo red and retained the stain only if the specimen originated from an animal with dysproteinaemia due to tumour, lead poisoning, non-specific inflammatory processes, etc. This observation is further supported by the following. The elastic elements of the small vessels, the skin and the lungs assume a dark blue colour on staining with Azan, just as collagen fibres. Congophilic fibres which have adsorbed paraprotein take a brilliant sky-blue colour with Azan, in sharp contrast against the dark blue vascular walls. Alone the elastic fibres appearing sky blue are capable of staining with Congo red, proving thereby that some foreign substance had become adsorbed to them. *It may be observed again and again that immediately beside the tumour the homogeneous substance stains with Congo red, while a little farther off it takes up only elastic dyes.*

We believe, in agreement with *Loeschke*, *Lehmann—Facius*, *Letterer* and his school, *Schneider*, *Gindin* and *Glebova*, that the appearance of amyloid around tumours is due to an antigen-antibody reaction, the antigen being supplied by the carcinomatous protein, while antibodies are probably produced by the organism with the intervention of plasma cells, partly locally, and partly, as seen in animal

experiments, in remote organs. The fact, that a substance staining with Congo red is formed in antigen-antibody reactions was proved by the following experiment.

0,1 ml of sheep serum was injected intradermally into a rabbit. Around the site of the injection homologous rabbit immune-serum was injected intradermally. The nodules resulting were excised 3, 12, 34 hours, respectively 2, 3, 5 and 12 days later and worked up histologically. Well-marked migration of white blood corpuscles around a larger centre was observed in the first preparation already, and in the leucocytes granules staining intensely with Congo red. The process was most marked after 24 hours, with a great number of white blood cells accumulated around a centre and very marked oedema extending farther on. With Congo red the granules in the leucocytes stained intensely. They did not stain with methyl violet, while with Azan both the granules in the leucocytes, and the oedematous fluid stained red. The collagen bundles were blue and increased in size. The granules did not stain with elastica. Two or three days later the oedema decreased considerably, the infiltration was still fairly marked. 5 to 7 days later, the oedema disappeared, the infiltratation decreased considerably. White blood cells filled with granules staining with Congo red were seated in both the infiltration and around the small lymph ducts situated nearer to the epithelium. On the 7th day local changes disappeared, only under the epithelium and around the lymph ducts of the papillary bodies were present groups consisting of 4 to 5 white blood cells laden with the above described granules. On the 12th day also the white blood cells disappeared. The white blood cells in question were not eosinophilic granulocytes.

From this experiments it follows that part of the paraprotein originating from the antibody-antigen reaction becomes phagocyted by white blood cells. The substance reacts positively to Congo red but in its fresh stage it stains red with Azan. Since the phagocyted substance is carried away by white blood cells through the lymph ducts and there is no further antigen available, the adsorption to elastic fibres and the subsequent ripening process of the substance cannot be observed under the above mentioned experimental conditions.

Additional observations seemed to show that the adsorption of paraprotein giving amyloid reactions is preceded — at least in certain cases — by an increase in amount of elastic substances. We observed in mammary and especially in skin cancers that the homogenous or filamentous structures, filling the whole papillary body and invading the stroma of the tumour, and staining adequately with eosin and van Gieson's stain, *proved to be elastic lamellae and fibres and did not yet give amyloid reactions.* It is, accordingly, possible that the appearance of elastic amyloid was preceded, — perhaps in every case — by an increase in the amount of elastic elements, which, for instance in scirrhus, may proceed parallel with the tumorous increase in the amount of connective tissue. Finally, most remarkable were the cases, for instance basal cell or squamous cancers of the skin, in which in areas quite remote from the tumour, such a marked elastosis of the subcutaneous connective tissue occurred without amyloid reaction, as in the immediate neighbourhood of the tumour itself *(Gruber, Miller, Farkas).*

Literary data, too, bear witness to this phenomenon. *Awoki* found destruction of the normal elastic system in the skin of aged persons and subjects suffering from arteriosclerosis or tumour, and observed in its place the appearance of rigid trabecular forms and clumps staining with elastica stains. *Ohno* found similar changes in the facial skin of old persons and called attention to the staining with

Sudan and Nile blue of elastic elements. It is well-known that *Roffo* found in the so-called »seaman's skin«, exposed to the vicissitudes of weather, a considerable increase in cholesterol. Remarkable are the observations of *Waljashko* who in cases of fibrous cancer of the breast observed, along with the destruction of elastic elements, also their increase in amount. This he thought to originate from the elastic substance of the ducts, the vessels and the glands. *Waljashko* did not carry out amyloid reactions, nevertheless it seems probable that he observed a phenomenon similar to the one noticed by us.

The same can be said of the observations of *G. B. Gruber*, who some years ago described under the term »mammary elastosis« increased elastic masses, occurring as well in the walls of the veins as around them, and around the milk ducts. He could present no adequate explanation, but thought that mechanical factors are chiefly responsible for the phenomenon. These factors would manifest themselves with a thickening of the vessels compressed by the tumour, and with the narrowing and occlusion of the lumina. He did not perform amyloid stainings.

Starting from the examinations of *Gruber*, *J. Miller* observed *»elastosis of the skin«*. Citing *M. B. Schmidt*, *Miller* described the above mentioned changes in the otherwise normal skin covering mammary tumours. Miller did not perform amyloid reactions either, and thus the possibility that at least one of his cases might have belonged to the group of elastic amyloidoses cannot be excluded. Remarkable is his observation that after a time the elastic lamellae lost their staining capacity and change into elacin. In our own cases we succeeded once in detecting elacin in a mammary tumour but only in the vicinity of the masses of elastic amyloid. *Miller* thought that in doubtful cases the appearance of elastosis would be indicative of cancer. Other authors, such as *Waljashko*, *Arzt*, denied this assumption. The changes are by no means specific, because, as mentioned above, *Teilum* probably observed the same process in some types of collagen vascular disease, such as erythematodes, etc., and we ourselves have seen it to occur in Boeck's sarcoid, and in periarteriitis nodosa. However, we never observed it around sarcomas. The appearance of elastic amyloid, although certainly not of a specific character, is in doubtful cases none the less indicative of malignancy.

Numerous authors have studied the role of plasma cells in the formation of blood protein of coarser dispersion, particularly of globulin, and parallel with that, of antibodies. (For the literature, see *Bernáth)*. According to *Apitz* plasma cells constitute a protein-forming system equivalent to the reticuloendothelial system, the liver and the bone marrow. It was *Bartha* who has called attention to the fact that in certain cases when, in contrast with expectation, the number of plasma cells is not increased, in the bone marrow smear they usually exhibit structural changes. In our first cases *Bernáth*, too, found an increase in the number of plasma cells and since then we have observed this phenomenon in some further patients. It may be assumed, that in cases in which at the time of the appearance of elastic amyloid plasma cells could no longer be met with, they had been

present only at the onset of the process. *(Apitz.)* It is of importance that their appearance is correlated with the formation of antibodies, as shown by the recent experiments of *Chun-Chang* and *Chi-Luen-Se*, carried out with typhoid vaccine. Accordingly, antibodies containing plasma cells with a foamy cytoplasm and sometimes with a ruptured membrane are stored also by serous membranes, e. g. the omentum. It is a relevant fact that the normal colloidal conditions of the blood plasma are disturbed and that in the range of globulins an increase occurs, corresponding to antibody production *(Letterer)*. According to the experiments of *Bohle*, *Hartmann* and *Pola*, a disturbance of normal colloidal equilibrium is the condition of amyloid precipitation, inasmuch as from among animals treated with yeast nucleinic acid those have developed amyloidosis in which the electrophoretic pattern showed the highest increase in the amount of gamma globulin.

In former studies we have repeatedly described the single factors of the defensive syndrome of the cancerous organism. To these belong, first of all, the changes in the »milieu interne« frequently appearing often as early as in the pre-carcinomatous stage, manifesting themselves in alkalosis, influctuations of the reserve alkali, in increased secretion of thyreotropic, melanophoric and gonadotropic hormones, in consecutive hyperthyreosis, in increased tone level of the vegetative nervous system and its increased sensitivity to adrenalin, insulin and oxygen. All these functions are under central neurohormonal control, as well as the alterations in the composition of blood plasma. *(Wuhrmann.)* The same refers to the mucopolysaccharides of the connective tissues, of the fibres and of the cells *(Brux* and *Boistesselin)*, as well as to antigen-antibody reactions *(Speransky)*. Amyloidlike substances such as fibrinoid, mucin, or hyaline, are after all depolymerized forms of these glycoproteins. (We have to point out that the amorphous elastic amyloid, and, according to *Altschuler* and *Angevine*, also the secondary amyloid, contain parts giving a positive Schiff reaction and staining lightly with methyl green).

Apart from the changes mentioned, according to *Brux* and *Boistesselin*, desoxycorticosterone and testosterone also raise the amount of glycoproteins in the connective tissue. And what is more, in consequence of their action, the collagen bundles may stain with Congo red and amyloid-like areas may appear. It is most probable that this action proceeds parallel also with antibody formation.

According to the literary data enumerated and our own observations *we consider in cases of cancer the appearance of the specific substance termed »elastic amyloid« as a product of an antigen-antibody reaction and as the morphological expression of this reaction, and believe that it may be ranged into the defensive syndrome of the carcinomatous organism.*

Summary

In numerous cases of cancer of the breast, of the skin, in parotid tumours, in adenocarcinoma and lung carcinoma a substance was observed which stained a homogeneous red with eosin, yellowish-brown with van Gieson's stain and which, on staining with Congo red, assumed in each case a brownish-red colour; metachromasia on staining with methyl-violet, polychrome methylene blue or iodine green did not result systematically. This substance giving amyloid reactions appears in large nodes, bands, or in broad lamellae. Around its homogeneous masses freshly precipitated material is seen in the form of fragmented, frequently greatly twisted fibres. Both the fibres and the homogeneous masses stain intensely with elastic dyes. After digestion with elastase they do not any more stain with Congo red or elastic stains. Neither the organs from cases of secondary amyloid, nor the so-called local amyloid tumours stain with elastic stains, nor are they digestible. Additional histochemical differences between common amyloid and the »elastic amyloid« described are the lack of dichroic staining on treatment with Congo red, and the peculiar blue, yellow or red colour assumed on staining with Azan. The initial phases of the process were examined in animal experiments; increased destruction of protein was brought about by exposing the inoculated tumours to X ray irradiation. The appearance of amyloid in tumours is believed to be a result of an antigen-antibody reaction in which the antigen is supplied by the carcinomatous protein. It is thought that the appearance of the substance termed *elastic amyloid* is a product of an antigen-antibody reaction being the morphological expression of it, and that the process belongs to the defensive syndrome of the carcinomatous organism.

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ДАЛЬНЕЙШИЕ ИССЛЕДОВАНИЯ К ВОПРОСУ АМИЛОЙДА, НАХОДЯЩЕГОСЯ В ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЯХ

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Р е з ю м е

Авторы во многих опухолях молочной железы и кожи, околоушной железы, во многих случаях аденокарциномы и рака легких нашли вещество, красящееся еозином в однородный красный цвет, а по ван Гизону в желто-коричневый цвет. Вещество конгоротом красилось в каждом случае в коричневый красный цвет; метилвиолетом, полихромной метиленовой синькой или иодгрюном метахроматическая реакция то получалась, то нет. Данное вещество, дающее положительную реакцию на амилоид, встречается в виде грубых глыбок, тяжей, в широких пластах под эпителием кожи.

Вокруг однородной массы видно и более молодые фазы отложения в виде отрывистых, часто круто извилитых нитей и волокон. Как эти волокна, так и однородные массы резко окрашиваются на эластин и после переварения эластазой потеряют как положительную окраску конгоротом, так и окраску на эластин. Органы больных страдающих вторичным амилоидозом, и т. н. местные амилоидные опухоли не окрашиваются эластикой и не потеряют окраску конгоротом после переварения эластазой. Дальнейшей гистологической разницей между обыкновенным амилоидом и описанным здесь »эластичным« амилоидом является отсутствие дихройческой окраски конгоротом и окрашаемость азаном в своеобразный синий, желтый или красный цвет.

Начальные стадии процесса изучались в экспериментах над животными: усиленный распад белков вызвался рентгеновским облучением перевиваемых опухолей.

По мнению авторов появление амилоида в опухолях вызывается реакцией антигенов с антителами. Антигеном служит раковый белок. Появление вещества, названного авторами »эластичным амилоидом« они считают следствием реакции антигена с антителом, — морфологическим проявлением этой реакции и осматривают данное явление как часть общей синдромы сопротивления организма против рака.