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MUCOPOLYSACCHARIDES IN THE HISTOCHEMISTRY OF CANCER

PRODUCTION OF NEUTRAL MUCOPOLYSACCHARIDES AND THEIR DRAINAGE THROUGH DILATED LYMPHATICS IN MOUSE CANCER C_3H

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According to our recent observations (Berencsi and Krompecher [3]), large quantities of what are apparently mucopolysaccharides can be demonstrated by histochemical methods in tuberculous tissue. Fermentation and chemical tests then disclosed in that tissue acid mucopolysaccharides and remarkable amounts of neutral mucopolysaccharides. On the basis of theoretical considerations supported in part by that experimental evidence we believe that the mucopolysaccharides are produced in tissues with altered metabolism, notably in such areas in which oxybiosis is replaced by metabolism involving anaerobic glycolysis. We think namely that in tissues that may suffer more or less marked necrobiosis under given conditions, normal metabolism is not replaced directly by necrobiosis, but various steps follow each other. Oxybiosis is followed first by hypoxia, then anaerobic glycolysis replaces aerobic glycolysis in the catabolism of sugars and it is only then that necrobiosis ensues. Thus large amounts of mucopolysaccharides may be expected to appear in areas where anaerobic glycolysis, the metabolic phase preceding local necrobiosis, prevails. This is why topographically the mucopolysaccharides occur in the area of necrobiosis and in the parts adjacent to it. In our work referred to above we have pointed out that the mucopolysaccharides produced in the tissue focus are drained away through the interspaces, and chiefly through the lymphatics accompanying the blood vessels into the blood stream, elevating the blood level of mucopolysaccharides. Thus in every condition in which the focus produces large quantities of mucopolysaccharides, the blood mucopolysaccharide level is significantly increased. Within certain limits, the blood mucopolysaccharide level reflects the activity of the focus or the foci, because the intensity of inflammation and of necrobiosis will decide the rate and intensity of mucopolysaccharide production by the focus.

The statements concerning tuberculosis should be valid also for cancer. In cancerous tissues namely — depending apparently on its poor blood supply — anaerobic glycolysis becomes predominant and more or less ex-

tensive necrobiosis may occur. One may therefore expect in or around cancerous tissues increased quantities of mucopolysaccharides to be demonstrated by histochemical methods.

* * *

We used the mouse strain C_3H. The sections embedded in paraffine were stained with haematoxylin eosin, according to VAN GIESON and RITTER-OLESON [35] and with toluidine blue. Staining according to RITTER-OLESON consists in the simultaneous application of HALE's stain [11] and the periodic acid-SCHIFF (PAS) stain. To prove that the material staining red with PAS is of carbohydrate nature, we performed the acetylation (blocking) test, and desacetylation with KOH. Prior to staining with PAS the sections were digested *lege artis* in pepsin or trypsin, to rule out that the material was of protein nature; MILLON's test was carried out. The sections were digested with diastase and saliva, to rule out glycogen. To eliminate lipids, the 8-micron sections were soaked 15 minutes in absolute ether, or absolute alcohol and stained with Sudan black. Digestion with BANGA's mucase 213/F3 was also made. As expected, staining according to RITTER-OLESON demonstrated the presence of large amounts of mucopolysaccharides (presumably neutral) in the sections of cancerous tissue. The gland-like structure formed by the tumour usually contained a strongly PAS positive substance in their lumina *(Fig. 1)*. The high-power appearance of the section of mouse cancer C_3H shows clearly that the PAS positive material in the lumina is continuous with the red material appearing in the interspaces of the neoplastic tissue. One has the impression as if the PAS positive substance collecting in the interspaces were flowing toward and accumulating in the lumen *(Fig. 2)*. Some of the gland-like lumina may dilate to a cyst-like cavity *(Fig. 3)*; their contents are strongly PAS positive *(Fig. 4)*. In some areas of the tumour PAS positivity tends to occur in the interspaces and is less marked in the lumina *(Fig. 5)*. At other sites the Prussian blue reaction of HALE [11] preponderates over the PAS positivity presumably indicating the presence of acid-mucopolysaccharides *(Fig. 6)*. In the PAS positive areas or near the PAS positive pools vessels accompanying the small arteries are remarkably dilated and the lymph in them is definitely PAS positive *(Fig. 7)*. This material, however, does not show metachromasia, at least when recently fixed. On the basis of the above this picture may be interpreted as showing that the mucopolysaccharides in the neoplastic focus are carried away in the lymph from the site of their production. As a natural result of this may be considered the well-known observation that in cancer, especially when the tumour is disintegrating, the blood mucopolysaccharide level is significantly elevated [6, 40, 41].

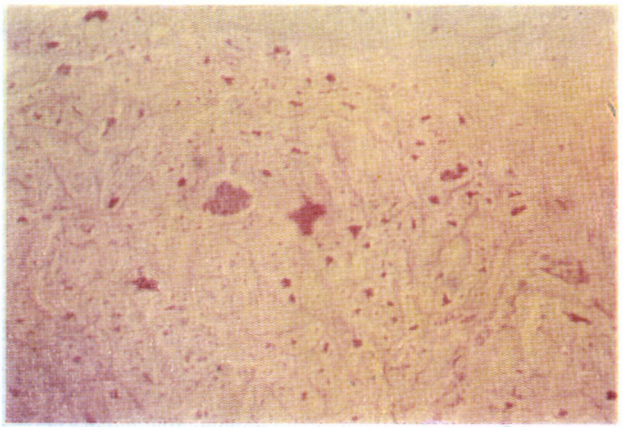

Fig. 1. Red PAS-positive material in the lumen of the cyst-like structure of mouse cancer C_3H

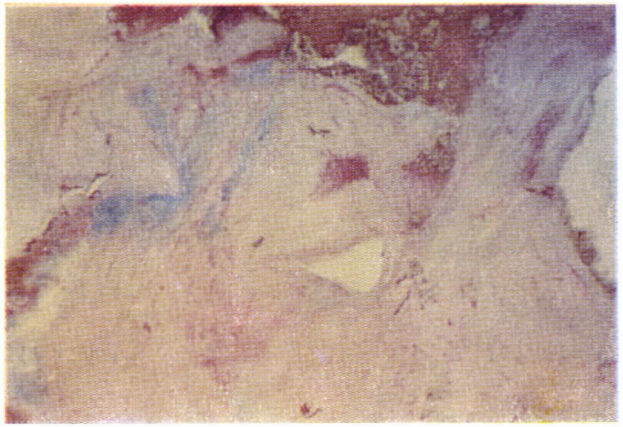

Fig. 2. PAS-positive substance collecting in the tissue interspaces in the direction of the lumenlike centre in regressive areas of mouse cancer C_3H

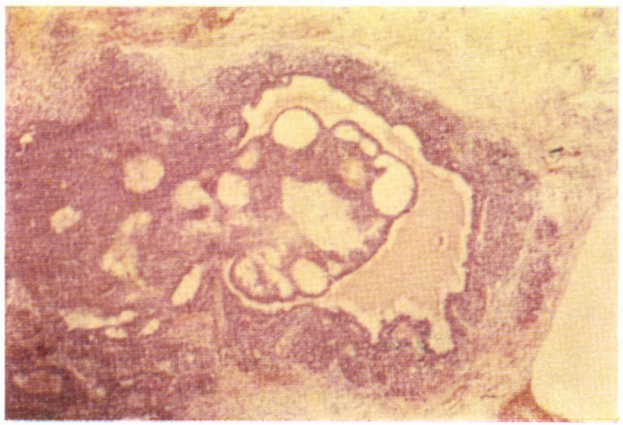

Fig. 3. Colloid-like material staining faintly with haematoxylin-eosin in the cyst-like lumen bordered by gland cells.

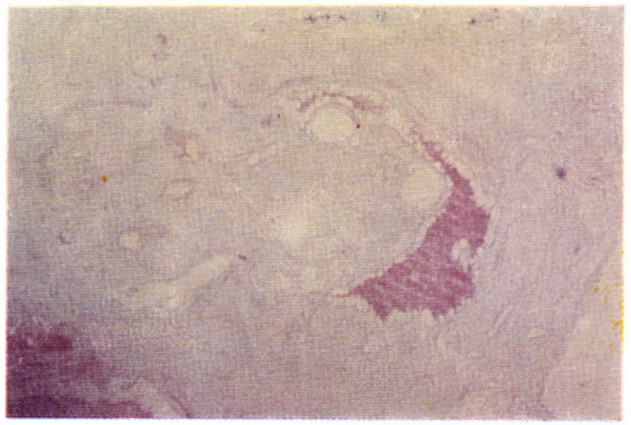

Fig. 4. Marked PAS-positivity of the material in the lumen; section next to that shown in Fig. 3

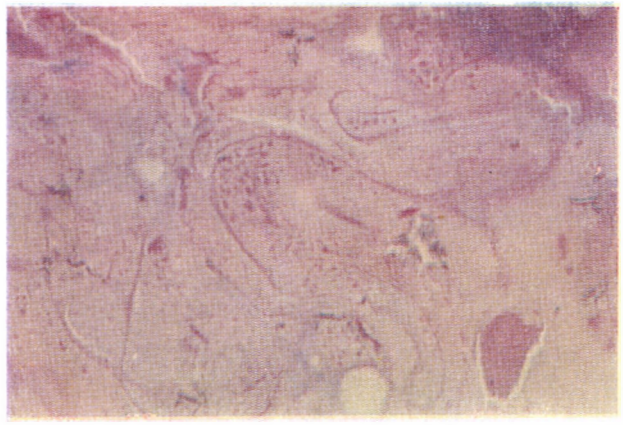

Fig. 5. In the central areas of the tumour that contain no capillaries and show regressive changes, large amounts of PAS-positive material are seen in the interspaces and in the lymph vessels

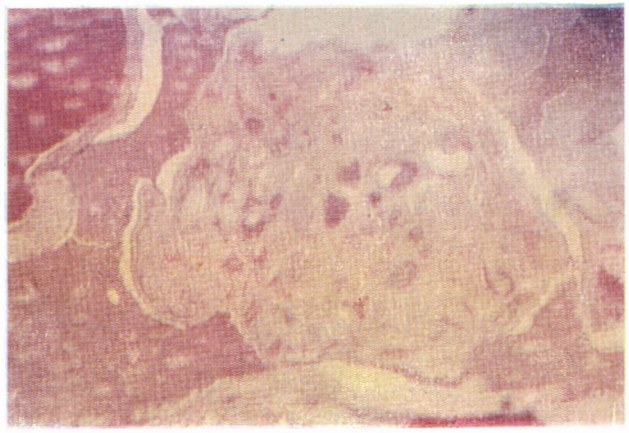

Fig. 6. In some areas blue Hale-positive material collects, instead of the PAS-positive substance

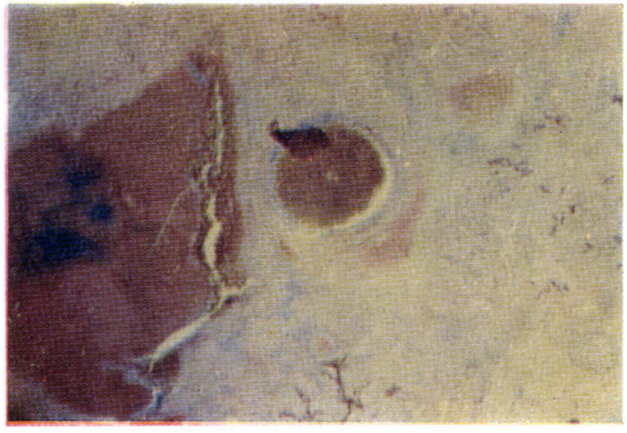

Fig. 7. Dilated lymphatic vessels filled with PAS-positive substance adjacent to the necrotic centre of mouse cancer C_3H

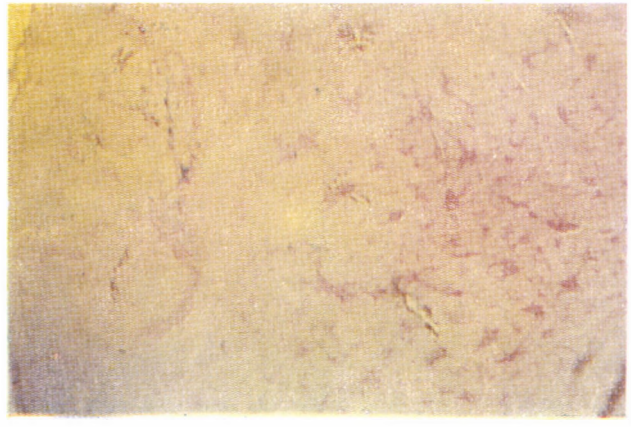

Fig. 8. Small amounts of PAS-positive material in the marginal areas of mouse cancer C_3H, that are relatively well vascularized and do not show regressive changes. More centrally, there is no capillary network, regressive changes are conspicuous and the PAS-positive material is present in large quantities

LENGYEL and SZEMESI [27, 28] have recently reported that in contrast with the surrounding normal tissue the smaller nests of tumour at the periphery of the neoplastic growth are surrounded by metachromatic, in other words acid, mucopolysaccharides. We, too, found no or very little metachromatic material in the centre of the tumour, while we succeeded in demonstrating large quantities of non-metachromatic neutral mucopolysaccharides in the centre of the tumour, as opposed to the marginal areas poor in PAS positive substance, where the capillary supply of the neoplastic tissue is good and thus metabolism is in all probability oxybiotic *(Fig. 8)*.

In this connection we should point out that according to SÜMEGI, GORECZKY and RÓTH [36, 37] in cancerous tissues an "elastic amyloid" would appear that is non-specific in nature and is ultimately a depolymerized glycoprotein. We think the said results lend support to our findings. These are further the observations by MOCHIZUKI [33] concerning the three types of PAS positivity and those reported by Soviet authors, first of all by AVERBAKH [1], who pointed out among others that the breast contains mucoids under physiological conditions, but an accumulation of mucoid occurs especially when there are fast-growing neoplastic foci in the breast. The more fast the malignant tumour grows the more mucoid it contains. AVERBAKH cites LAZOVSKI and others who stated that tissue hypoxia or anoxia would cause the accumulation of mucoids. Mucoids appear in the affected areas also in experimental hypoxia, serous oedema and when venous circulation is impaired. According to LAZOVSKI, mucoids may occur under physiologic conditions in areas poorly or not vascularized, for example in the valves of the heart, in which he thinks there is relative hypoxia. Thus, the appearance of mucoid may be traced back first of all to a disturbance in oxydative processes, to a preponderance of glycolytic processes. This is in harmony with the well-known fact that there is anoxia around tumours and there the glycolitic processes usually preponderate (OKUNIEV, NEUMANN and others [1]).

The presence of mucin-like substances in cancer tissue is not a new discovery. For example, E. KROMPECHER as early as around the turn of the century demonstrated mucoid in the interspaces of basal-cell cancer, eventually also in its cyst-like cavities, as well as in the connective tissue stroma around the cancerous tissue [21, 22, 24]. E. KROMPECHER [21] called this substance pseudomucin, as according to his investigations published in 1903 it showed no metachromasia [21, 22]. We can confirm this but have further developed the statement mad · n ore than half a century ago. The histologists of the turn of the century did not go further than to claim that the mucin in cancer tissue was a degeneration product. Our investigations, aided by improved methods and by a comparison with other evidence, have supplied data concerning the biochemistry of mucopolysaccharide formation and contributed to a better understanding of the problems involved.

Mucin formation may occur also in cancer of the lung; BALÓ [2] described and illustrated impressive cases of HAMPERL's [12] mucin granulomatosis.

Have the mucopolysaccharides arising in neoplastic tissue some influence on the malignancy of the tumour, or in other words, do they influence the relation between the tumour and the host organism? It is imperative to take this possibility into account, as mucin is known significantly to enhance the virulence of various microorganisms (bacteria, viruses [3]). It is therefore quite possible that mucopolysaccharides may increase what E. KROMPECHER [22] called the virulence of tumour cells. Some authors claim that the mucin formed would be a material into which the tumour may grow and along which it may proliferate. Thus, the mucin in the environment of cancer may increase the expansivity of the neoplasm. E. KROMPECHER [22] was also of this view while DELBOT and MENDARO [7], as well as DELBOT and HERRENSCHMIDT [8] are of the opposite opinion. According to them, tumours secreting mucin are relatively benign, as 48 per cent of the patients who had been operated for such tumours were found to be free from recurrence 5 years after operation. LEROUX and PERROT [30] share this view. BERTRAND and NAGY [4] do not consider this mucin production a sign of prognostic value and a similar conclusion has been drawn by FRANTZ [10] from 130 radically operated and histologically studied cases of cancer of the breast.

Thus the problem has not been solved; its clarification is a promising task since the mucopolysaccharide milieu (which according to E. KROMPECHER enhances expansivity), the modification of virulence by mucopolysaccharides (which protect the cancer cells against defensive forces of the host), and the close correlation between mucopolysaccharide production and tissue necrobiosis cannot be independent of the tumour's malignancy, and might therefore be of a prognostic significance. There is every reason to believe that careful studies will ultimately demonstrate the correlation.

We attribute particular significance in the formation of metastases to the disjunction of cancer cells from cancerous tissue, to tissue necrobiosis and to the eventual role of the mucopolysaccharide milieu. As early as 1913 E. KROMPECHER [23] stated: "The detachment of these epithelial cells and their propagation by infiltration actually constitute local metastases, which do not differ in principle from the subsequent formation of secondary deposits in more distant organs". . . "I think that the rapid spread of melanocarcinoma and formation of extensive metastases might be due to an increased rate of detachment of epithelial cells resulting from disintegration caused by pigmentation, which so creates more favourable conditions for the spread of the tumour." KELLNER [14—20] also ascribed great importance to cell disjunction in the cancerous focus and to the necrobiosis promoting it.

It may be asked whether one is justified in claiming the material present

in considerable quantities in mouse cancer C_3H to be neutral mucopolysaccharide. Is this material definable chemically, can it be differentiated from other materials, can we follow its formation, spread and accumulation? Can we detect its presence in the various stages of embryonic, postembryonic life, or in different pathological conditions? Recently we have succeeded in establishing some facts concerning the nature of the material we call neutral polysaccharide, as in our studies of embryonic and postembryonic cartilage breakdown, regenerative and neodifferentiative cartilage formation [9], exsudative pulmonary tuberculosis [3], crural ulcer [26], as well as mouse cancer C_3H. They are as follows.

1. The material in question is PAS positive, *i. e.* it stains red by the periodic acid-Schiff method. By the RITTER-OLESON technique it stains red, while the acid mucopolysaccharides stain blue.

2. The red staining does not appear after blocking by acetylation, and reappears when desacetylation is effected by treatment with KOH.

3. The PAS positivity is not lost after previous digestion with pepsin or trypsin.

4. The same applies to pretreatment with lipid solvents.

5. The PAS positive areas give a weak Millon reaction, and

6. are lightly stained by Sudan black.

7. The material supposed to be neutral mucopolysaccharide shows no metachromasia to toluidine blue, as opposed to the acid mucopolysaccharides which stain purple with that dye. For example, the material presumed to be heparin, that can be found in the mast cells of the skin over the mouse cancer, stains red.

8. On biochemical identification the material in question was dissolved in a few hours by mucase 213/F3, at pH 7.4, 37° C, in a n/40 veronal acetate buffer solution. During the same period the buffer system not containing mucase caused no change in staining. This means that the phenomenon is a true mucase effect.

9. As to the biological or pathological characteristics, it may be stated that the material is produced when tissues are disintegrating.

Large quantities of the material are formed in disintegrating exsudative caseous pulmonary tuberculosis [3], in the areas of the mouse cancer C_3H that show regression or disintegration, as well as in crural ulcers [26]. Thus, the material is produced where tissues are broken down or disintegrating, under both physiological and pathological conditions (cartilage [25], connective tissue, lung tissue, cancer).

If we look for the cause of tissue disintegration, local vascular changes and the hypoxia will feature prominently, both in the neodifferentiative cartilage formation, and in the three pathological conditions (tuberculosis, cancer, crural ulcer) examined.

As to physical characteristics, the material in question is highly viscous and liquid.

From the pathophysiological point of view it seems to be characteristic that the material formed in large quantities at the site of tissue disintegration is drained off through the lymphatics, which thus become dilated. This is apparently of significance in paving the way for the formation of metastases. The PAS positive substance can be demonstrated in both the cross and longitudinal sections of the lymphatics.

It is known from the literature, WINTZLER [40], WOLSTENHOLME and O'CONNOR [41] that in grave pulmonary tuberculosis, in cancer and other conditions the blood mucopolysaccharide level is significantly increased to 1.5 or even 2.5 times the normal, which is around 83 $\pm$ 4 mg per 100 ml. expressed in hexosamine.

The elevation of the serum mucopolysaccharide level in pulmonary tuberculosis to 1.5—2 times the normal level has been confirmed by EVA H. OLÁH, biochemist, in 70 determinations made in 45 subjects. She worked at the Institute of Anatomy, Histology and Embryology of the University Medical School of Debrecen, in cooperation with the Department of Tuberculosis.

As opposed to these positive data, we do not know the exact chemical structure of neutral mucopolysaccharides. It is not known whether the mucopolysaccharides found in the blood in cases of cancer, tuberculosis and similar conditions differ in structure, or in the glucosamine : galactosamine ratio. Still, the material may rather reliably be characterized on the basis of its histochemical (PAS positivity, negative metachromasia, acetylation, Millon reaction, Sudan staining, lipid solvents), biochemical (dissolution in mucase, pepsin, trypsin digestion), and pathological properties (occurrence at the site of tissue decomposition) as well as by the fact that its drainage through the lymphatics and accumulation in the blood can be followed up.

We have also studied the vascularization of mouse cancer C_3H. As it is shown by *Fig. 8*, the marginal, actively growing area of the tumour is satisfactorily vascularized. In that area there is hardly any, or no evidence of regressive tissue changes, neutral mucopolysaccharide production, or disjunction of cells. In contrast with this, in more central areas of the tumour vascularization is scarce or absent. Here the cells show regressive changes and neutral mucopolysaccharides are formed in large amounts. There are then the necrotic areas, in which blood vessels do not occur at all. We cannot speak of vascularization in such areas, though haemorrhages with haemosiderin formation originating from arroded blood vessels may occur. Thus, in a cancerous tumour we may distinguish between three zones, *viz.* (i) a PAS negative zone, with a relatively good blood supply and without tissue disintegration; (ii)

a PAS positive zone showing tissue regression, with a relatively poor vascular supply; and (iii) a zone of necrosis, without vascularization.

Considering the above, tissue hypoxybiosis is probably responsible for the formation of mucopolysaccharides in cancer tissue. In hypoxybiosis anaerobic glycolysis gains preponderance. This phenomenon might be part of some function which, perhaps as an atavistic trait of metabolism, takes effect in every instance of deficient oxygen supply. In other words, the living tissue tries to adapt itself to the lack of oxygen by breaking down sugar by the anaerobic mechanism. In this case the described production of mucopolysaccharides is a result of tissue adaptation, and plays a role in every condition in which adaptation to a deficiency in oxygen is involved. According to WEINHOUSE [39] cancer tissue and cancer cells possess a high aerobic and anaerobic glycolytic activity. For example, in the presence of oxygen cancer tissue can break down several times the amount of sugar broken down by resting or growing normal tissues. The more deficient the oxygen, the less marked the difference between cancerous and normal tissue, and under anaerobic conditions the difference is not more than ¼ to 3.5. According to WARBURG [38], the anaerobic glycolysis of cancerous tissue is characteristic of malignancy. We believe that a poor or absent vascular supply creates the conditions (hypoxybiosis, anoxybiosis), which cause cancerous tissue to adapt itself to the new milieu and switch over to anaerobic glycolysis, as a result of which mucopolysaccharide production is begun. Thus, the anaerobic glycolysis of cancer tissue is not just one characteristic property, but it is the result of a general biological law, of the adaptation to hypoxia. The described production of mucopolysaccharides may be interpreted in this way.

LE PAGE [29], as well as NOVIKOFF, POTTER and LE PAGE [34] have arrived at the conclusion that in tumours anaerobic glycolysis is based on the known EMBDEN—MAYERHOF scheme, *i. e.* it is not different from that in normal tissue. MEYERHOF et al. [31, 32] essentially confirmed that there is no qualitative difference in lactic acid formation between normal and tumour cells. WEINHOUSE [39] postulated that there is no evidence at present to show that glucose would be broken down to lactic acid in tumour tissue by a mechanism different from that in normal tissue. According to BURK [5], there is no difference in oxygen consumption between the cancerous liver cell and embryonic, aged, regenerating or cirrhotic liver cells. And if there is no difference in the mechanism of lactic acid fermentation between cancer and normal cells, why should there be a difference in the factors eliciting it?

Volumes have been filled with metabolic studies in cancer research and a number of valuable data have been published, yet we have very little exact knowledge as to the essence of the pathology of cancer.

According to WEINHOUSE [39], we should know the factors controlling and regulating cell metabolism in order to understand the excessive rate of

glycolysis in neoplastic tissue. He deems it unfortunate that we know so little about such factors. In this connection we call attention to the metabolism and vascular pauperisation of cancer tissue, as well as to the hypoxydosis resulting from them. Let it finally mention that in addition to the above we have succeeded in demonstrating the formation of mucopolysaccharides in human gastric and pulmonary cancer, as well as in tar cancer of the rabbit ear.

Summary

Sections of mouse cancer C_3H were treated by RITTER-OLESON's histochemical method demonstrating simultaneously the neutral mucopolysaccharides (by the periodic acid—SCHIFF reaction) and the acid mucopolysaccharides (by HALE's method). A material supposed to be neutral mucopolysaccharide has thus been demonstrated in considerable quantities. In the marginal areas of cancer tissue, which have a relatively good vascular supply and growing, no neutral mucopolysaccharide formation was demonstrable. In contrast with this, in areas with poor vascular supply, lying centrally and thus supplied poorly by diffusion, increased neutral mucopolysaccharide formation was observed. In the necrotic central parts of large tumours were the greatest quantities of neutral mucopolysaccharide found. It is concluded that the mucopolysaccharides are produced in the hypoxybiotic phase of the adaptive metabolic changes of cancer tissue (oxybiosis, hypoxybiosis, anoxybiosis, necrobiosis), when anaerobic glycolysis gains preponderance. In the relatively well vascularized areas of cancer tissue acid mucopolysaccharides, in the poorly supplied areas neutral mucopolysaccharides are formed. These neutral mucopolysaccharides arise when tissues are decomposing, disintegrating, as in the tuberculous foci. From their site of production the neutral mucopolysaccharides are drained away through the tissue interspaces and lymphatics into the blood stream (preparing apparently the way for the formation of metastases); this explains the well-known observation that in cancer the blood mucopolysaccharide level is significantly increased, roughly in proportion to malignancy and necrobiosis. Thus, in cancer and tuberculosis the neutral mucopolysaccharides are not deposited from the blood into the affected tissues. On the contrary, they are produced in the tissues with anaerobic glycolytic metabolism and are carried away by the lymph into the blood stream. The mucopolysaccharides formed in cancer tissue may influence the relation of the cancer tissue to the host organism and modify the expansivity of cancer and the formation of metastases.

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МУКОПОЛИСАХАРИДЫ В ГИСТОХИМИИ РАКОВОЙ ТКАНИ

И. КРОМПЕХЕР и ДЬ. БЕРЕНЧИ

Симультанно были выявлены на срезах C_3H рака мышей с помощью гистохимического метода *Риттер—Олесона* нейтральные и кислые мукополисахариды, причем авторы в значительном количестве обнаружили вещество, предположительно соответствующее нейтральным мукополисахаридам. Образования нейтральных мукополисахаридов не наблюдалось в снабженных сосудами растущих краевых частях рака, однако, в плохо снабженных сосудами или же центрально расположенных и следовательно также и путем диффузии плохо снабженных частях наблюдалось все большее и большего раз-

мера образование нейтральных мукополисахаридов. В центральной части более больших опухолей наблюдаются некрозы; в области некрозов образование нейтральных мукополисахаридов больше всего. Предполагается, что мукополисахариды образуются в сильно гипоксибиозной фазе возникающих в раковой ткани изменений обмена веществ адаптационного характера — оксибиоз, гипоксибиоз, аноксибиоз, некробиоз, — а именно тогда, когда обмен веществ тканей изменяется таким образом, что расщепление сахара происходит путем анаэробного гликолиза. В сравнительно лучше снабженных краевых частях раковой опухоли образуются кислые, а в выраженно плохо снабженных частях — нейтральные мукополисахариды. Эти нейтральные мукополисахариды возникают при расщеплении, при распаде тканей, подобно процессам, имеющим место в туберкулезных тканевых очагах. Возникающие в значительном количестве нейтральные мукополисахариды попадают с места их производства через межтканевые щели и расширенные лимфатические сосуды в кровяное русло. Этим объясняется общеизвестное наблюдение, что в раковой опухоли содержание мукополисахаридов в крови значительно повышается, и что оно до известной степени пропорционально злокачественности и некробиозу. Значит, как в случае рака, так и туберкулеза, нейтральные мукополисахариды не отлагаются из крови в патологическую ткань, а они производятся в тканях с гипоксибиозным обменом веществ и анаэробным гликолизом, откуда они через лимфатические пути попадают в кровяное русло. Быть может, что вышеописанные мукополисахариды воздействуют также и на отношение между раковой тканью и организмом хозяина, модифицируя распространение раковой ткани и метастазирование.

MUCOPOLYSACCHARIDE IM KREBSGEWEBE

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An C_3H Mäusekrebsschnitten wurden mit der histochemischen Methode von RITTER-OLESON die neutralen und sauren Mucopolysaccharide simultan nachgewiesen, wobei ein vermutlich den neutralen Mucopolysacchariden entsprechender Stoff in bedeutender Menge gefunden wurde. Die Bildung neutraler Mucopolysaccharide konnte an den vaskulär gut versorgten und wachsenden Randteilen des Tumors nicht wahrgenommen werden. Dagegen war in den vaskulär schlecht versorgten, bzw. zentral gelegenen und infolgedessen auch durch Diffusion schlecht versorgten Teilen die Bildung von immer mehr neutralen Mucopolysacchariden zu beobachten. Der zentrale Teil von grösseren Geschwülsten enthält Nekrosen; im Umkreis derselben ist die Bildung von neutralen Mucopolysacchariden am grössten. Wahrscheinlich entstehen die Mucopolysaccharide in der stark hypoxybiotischen Phase der im Krebswege entstehenden Stoffwechselveränderungen adaptiven Charakters — Oxybiose, Hypoxybiose, Anoxybiose, Nekrobiose — und zwar dann, wenn der Stoffwechsel der Gewebe sich in der Weise verändert, dass der Zuckerabbau durch anaerobe Glykolyse erfolgt.

In den noch verhältnismässig gut ernährten Randteilen der Krebsgeschwulst entstehen saure, in den ausgesprochen schlecht ernährten Teilen neutrale Mucopolysaccharide. Diese letzteren entstehen beim Abbau, beim Zerfall der Gewebe, ähnlich wie in den tuberkulösen Herden. Die in bedeutender Menge produzierten neutralen Mucopolysaccharide gelangen vom Ort ihrer Entstehung durch die Gewebsspalten und durch die erweiterten Lymphgefässe in die Blutbahn. Hierdurch erklärt sich die allbekannte Beobachtung, wonach in der Krebsgeschwulst sich der Gehalt an Mucopolysacchariden im Blut bedeutend erhöht und bis zu einem gewissen Grad proportional zur Bösartigkeit und zur Nekrobiose ist. Demnach werden sowohl bei Krebs, wie auch bei Tuberkulose die neutralen Mucopolysaccharide nicht aus dem Blut in das pathologische Gewebe abgelagert, vielmehr erfolgt ihre Produktion in den Geweben mit hypoxybiotischen Stoffwechsel und anaerober Glykolyse, von wo sie durch die Lymphbahn in den Blutstrom gelangen. Es ist nicht ausgeschlossen, dass die beschriebenen Mucopolysaccharide auch auf das Verhältnis zwischen Krebsgewebe und Wirtsorganismus eine Wirkung ausüben, und somit die Expansivität des Krebsgewebes und die Metastasenbildung modifizieren.

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