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THE AGAR BINDING REACTION IN SKIN DISEASES

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The diagnostic method of CSABA and TÖRŐ, published in 1958, is based on the observation that agar becomes turbid if brought into contact with the serum of patients suffering from malignant tumour. According to the authors' theory, the malignant proliferating tumour cells break through the normal hyaluronic acid—heparin barrier, giving thus rise to the formation of depolymerizates, become attached to proteins, and induce the production of immune substances against themselves. Specific antibodies produced in the organism against mucopolysaccharides can be demonstrated by the turbidity of agar, a polysaccharide of vegetable origin which has a similar chemical structure.

CSABA and TÖRŐ obtained with their reaction (CsTR in the following) a positive result in 85.9 per cent of carcinomas, 60 per cent of sarcomas, 78.4 per cent of their cases of Hodgkin's disease and 90 per cent of melanomas, all histologically verified. They emphasized that the proportion of false negative reactions was especially high (26.8 per cent) in the group of superficial carcinomas (skin, vagina, vulva, larynx, lip, tongue). The serum of carcinomatous patients in the diffuse, final stage of the disease proved positive in 24 per cent, while a false positivity was observed in 12.8 per cent of the controls. Part of these false positive reactions has been attributed to lipemia, and it was attempted to avoid the misleading positive reactions by lipid-free diet. Animal experiments, performed by CSABA and KISS, yielded similar results; they encountered around the tumours numerous mast cells or free heparin granules and stated that their number was proportional to the positivity of the reaction. Such a direct relation is well borne out by the fact that the serum of rabbits (the connective tissues of which contain no mast cells) gives a negative reaction even after successful transplantation of tumours. Experiments *in vitro* disclosed that all negative sera become positive on adding 800 μ g of histamine, and that the same happens after treatment with 0.5 per cent protamine sulphate. Lipoproteins, specific for the reaction, remain latent as long as the equilibrium between heparin and histamine is maintained, and are released after the balance has been overthrown. According to the

authors, involved in the CsTR are lipoprotein-antigens with their antibodies and mucopolysaccharide-antigens with their antibodies of the properdin type; besides, the C_3 complement fraction and histamine seem to play a certain part. All these substances are present in normal serum; when malignant tumour is formed, their equilibrium is upset.

An increased number of mast cells around carcinomas was first observed by EHRLICH and confirmed later by WESTPHAL, FROMME, WEILL, STAEMMLER, HIGUCHI and QUENSEL, who pointed out that, while a particularly large number of mast cells appeared in the zone between the carcinoma and its intact surroundings, very few — or no — such cells were observed in the tumour itself. Mast cells are according to SYLVEN larger, and their granules more variable in and around the growing part of the tumour than in the areas of degeneration. On the other hand JANES and MCDONALD found only a few mast cells in the stroma of gastric, duodenal, sigmoid, rectal, mammary, renal, ureteral and prostata carcinomas and in lymphnode metastases, while they observed many mast cells in regional nodes which did not contain metastases; the number of mast cells in the stroma of gastric ulcers was four times that found in carcinomas. Studying melanotic cc-metastases, WEILL failed to find mast cells in the parenchymal organs but saw a great number in the lymphnodes and the surrounding connective tissues; he concluded that a mast cell reaction could occur only in tissues which contain mast cells under normal conditions. STAEMMLER claimed that the number of mast cells decreases if a tumour rich in connective tissue develops in a tissue which contains many mast cells as, for instance, in the case of fibroadenoma mammae. This has been confirmed by HIGUCHI who detected no mast cells in sarcomas. It was in the vicinity of skin carcinomas that ASBOE—HANSEN observed the increased amount of mast cells and hyaluronic acid. Numerous mast cells were found by LENGYEL and VÉRTES around the circumscribed cell nests of basal-celled carcinomas and the stroma assumed a metachromatical bright red colour. This colour disappeared under the influence of hyaluronidase, thus revealing the presence of hyaluronic acid. On the other hand, metachromasia was scarce and limited to a small area around the cell nests of spinocellular carcinomas. The different behaviour of the two types of tumour has led to the conclusion that hyaluronic acid constitutes an important factor of stromal defence; its increase around the basal cell nests restricts tumorous proliferation, while its considerably smaller amount around spinocellular carcinomas (a phenomenon presumably due to higher hyaluronidase activity) promotes spreading and metastasis. Increase in the amount of hyaluronic acid went hand in hand with an increase in the number of mast cells. This seems to support ASBOE—HANSEN's theory that hyaluronic acid is produced by the mast cells. LENGYEL and SZEMESI observed an abundance of hyaluronic acid around the small tumour-cell nests in the epithelial carcinoma of the

uterine cervix, but failed to do so in cases of large tumorous conglomerates poor in stroma: the amount of hyaluronic acid seems to depend on the proportion of stroma and parenchyma, as also on invasive growth. From the increased amount of hyaluronic acid around the stroma-rich, small spinocellular tumour-nests as also around epidermal and lymphnode metastases, SZEMESI and LENGYEL concluded that the phenomenon in question was determined not so much by the nature of the tumour cells as rather by the local reactivity of the stroma which latter is a function of the interaction between tumour and organism.

It was likewise in the stroma round the buds of basal-cell carcinomas that SWERDLOW observed intensive metachromasia in the overwhelming majority of his cases. It would seem as if the stroma formed an integral part of basal-cell tumours, growing together with the epithelium, while the stroma of spinocellular cancers, melanomas and metastatic tumours first resists invasion and is finally torn apart. Observations made on growing experimental tumours also point to the important role of mast cells. The formation of subepithelial mast-cell tumours was observed after the painting of the skin of white mice with tar (SCHREUSS, ROCA DE VINYALS), and the cutaneous and subcutaneous accumulation of mast cells after its painting with various carcinogenic substances (TWORT and TWORT): it was in proportion with the degree of the subepithelial inflammation and had grown until it became quite tumour-like. Investigations made by CRAMER and SIMPSON gave the result that the development of mast-cell reaction precedes the formation of tumours, and that it is more pronounced in animals resistant than in those sensitive to experimental tumours; the mast-cell reaction is a defence against carcinogenic stimuli, and it is the heparin contained in the mast cells that inhibits the increased hyaluronidase action in tumours (GLICK and SYLVÉN; GREENSTEIN). That heparin tends to inhibit tumoruos growth has been confirmed by several authors (HOLMGREN and WOLFHART, FISCHER, BALAZS and HOLMGREN, HARDING, HEILBRUNN and WILSON), although SZEMESI and LENGYEL failed to prevent tumorous growth in animals either with heparin or with hyaluronidase. Of fundamental significance is the statement of JORPES, HOLMGREN and WILANDER that in tissues the number of mast cells and the amount of heparin are in a direct ratio; it is moreover probably the irritative action of the growing tumour which increases the number of the mast cells and so the amount of heparin produced by these cells. This would mean that heparin plays a double role in the production of stromal reaction: (i) it is a precursor of hyaluronic acid (ASBOE—HANSEN); (ii) it inhibits hyaluronidase activity and so increases the viscosity of the interstitial space, while promoting — as a formative factor — the formation of connective tissue fibres. The concept that the principal function of the mast cells consists in the production of the ground substance of connective tissues (STAEMMLER, SYLVÉN, ASBOE-

HANSEN, BENSLEY, etc.) is supported by the results of WICHMANN who succeeded in demonstrating that in healing wounds the number of mast cells — after a decrease on the first day — grew gradually from the second day to reach its peak on the 8th to 10th day by which time fresh connective tissue had been formed. It might be assumed that a somewhat similar — though slower — process occurs in the initial phase of tumorous growth.

The theory that mast cells play a paramount role in the production of heparin seems to be contradicted by the fact that MENEGHINI, by repeated intra- and subepidermal injections of heparin and mucin derived from human umbilical cord, and PASCHOUD, by that of glucosamine, succeeded in producing mast-cell infiltration; that this is possible by means of heparin and mucin is, according to PASCHOUD, due to the fact that both these substances contain glucosamine either as a decomposition product or as contamination. Although it is likewise possible that the phenomenon is actually due to a storage in the fixed connective-tissue cells (BURKL), possibly a process of synthesis and no true accumulation of mast cells, the experimental results seem to indicate that the process in these cases is still more intricate and that — while heparin is produced by mast cells — heparin or glucosamine, its structural component, may somehow produce a formative stimulus and so facilitate the conglomeration of the ubiquitous mast cells.

Histamine is another product of the mast cells. Its amount is likewise proportional to the number of mast cells; it is especially high in animal mast-cell tumours and in human urticaria pigmentosa (RILEY and WEST; WEST). Heparin and histamine are supposed to form a complex in the granules of the mast cells from which they are liberated in allergen-antibody reactions as also in response to temperature, chemical and light stimuli. Histamine does not seem to play any role in fibrous reactions because structural changes in the peritumoral connective tissue are essentially different from the characteristic acute, exudative inflammatory symptoms induced by the liberation of histamine. Histamine, an antagonist of heparin and hyaluronic acid, while able to prevent the growth of connective-tissue fibres in a direct way, may probably do so also through the acute inflammatory oedema it provokes, *i. e.* by diluting and washing away the mucoid substances which are between — or attached to — the fibres, and so preventing their organisation. It may be due to the liberation of histamine and the development of oedema that the fibrous reaction is prevented in the circumscribed mast cell infiltrations of the skin in urticaria pigmentosa, although this would be more possible here than in the surroundings of epithelial tumours which are poorer in mast cells. The special histological features of the various types of animal mast cell tumours (dog, cat, ox) may be interpreted similarly. An analysis of HEAD's observations on a large material seems to make evident that the system of collagenous fibres is highly developed, thick and fascicular in those types which

are free from oedema (I*a*, I*c*, III, IV) and *vice versa:* the network is delicate and thin in oedematous stroma (types I*b* and II). The existence of transitory forms between the two types points likewise to a reciprocity of the two phenomena. Moreover, in tumours of this type it is not only the connective tissue-forming effect of hyaluronic acid which seems to be inhibited: the special anticoagulant action of heparin seems to be likewise suppressed, for as a rule no haemorrhages are demonstrable in the tumours themselves, nor does the blood of the tumorous animals reveal any anticoagulative action (REILLY). That coagulation is protracted after removal of the tumour may be due to the surgical injury (SCHWARTZMAN and ORKIN). By way of analogy, the haemorrhagic form of urticaria pigmentosa is likewise infrequent, and data on the patients coagulation time are contradictory.

The theoretical foundation of the CsTR and the said results have induced us to examine from a dermatological point of view its (i) diagnostic value; (ii) its connection with stromal reaction; (iii) its behaviour in other processes where the mast cell-heparin-hyaluronic acid system seems to have a significant role. It was hoped that such investigations would allow a deeper insight into inner relationship connected with the matter in question.

Method

We proceeded according to the technique described by CSABA and TÖRŐ; the dietary rules — established with a view to avoiding turbidity due to lipemia — as also those regarding medication (prohibition of veronal) were strictly observed. We had our results checked at the beginning by sending the sera (labelled with pseudonyms) to the Institute of Histology and Embryology where the procedure was repeated; as its findings were invariably in agreement with ours, we dispensed with regular checking in the later course of the experiments and contented ourselves with occasional controls. Likewise at the beginning, every reaction was repeatedly examined; since, however, there occurred neither doubtful nor contradictory results, later we repeated only such reactions where we wanted to ascertain the effect of some handling upon their positivity or degree. The reaction is quite clear readable, and both its weakening and strengthening are generally well visible.

We always began with the histological confirmation or correction of the clinical diagnosis and right from the beginning we strictly differentiated the types of epithelioma, the cases of precancerous conditions and incipient tumours. We employed haematoxylin-eosin or van Gieson's stain to study the penetration or demarcation, the nature and quantity of connective-tissue fibres, possible reactions of cellular inflammation and oedema; cresyl-violet was used for the study of acid polysaccharides, and toluidine-blue for that of mast cells. As regards fixing fluids, we dispensed with the use of the generally recommended basic lead acetate and Carnoy's fluid; in doing so, we were led by the consideration that mucosaccharides, the decisive factor of fibrous reaction, are incorporated in the fibres so that they are not or hardly washed away by fixation in formalin solutions, whereas a pathological accumulation of hyaluronic acid can only be inferred if it remains perceptible even after usual fixation in formalin. We did not make use of the hyaluronidase reaction which serves to distinguish hyaluronic acid from chondroitin-sulphuric acid B because the amount of the latter is negligible in the stromal reaction of tumours. We furthermore omitted to carry out a systematic examination of neutral mucopolysaccharides which would have only further complicated the elucidation of the intricate correlations.

Material

In order to determine the principal question, *i. e.* to ascertain the diagnostic value of the CsTR we selected our cases originally so as to be able to compare a group of carcinomatous patients with one composed of non-carcinomatous subjects. Therefore patients with various well-defined skin diseases were chosen as controls, and very few healthy persons were examined. Cutaneous processes in which the involvement of mast cells and hyaluronic acid had been recognized formed a separate group. This enabled us to obtain data which seemed suitable for the elucidation of certain questions. Likewise separate groups were formed of malignant systemic diseases; precancerous cases; other tumours; chronic and acute inflammations. In selecting our material, we did not lay especial stress on great numbers; what we wanted to obtain was a material composed of cases well defined both clinically and histologically and thoroughly examined in accordance with the nature of the disease; we also attempted to exclude patients suffering from cancer of some inner organ.

The number of our test cases was 201, of which 123 were males and 78 females; their age varied between 18 and 85 years with an average of 50 years. Fifty-two patients had epithelioma and 149 some other disease.

Results

The CsTR was positive in 34 cases of epithelioma, *i. e.* in 65.4 per cent of a total of 52 such cases. The history varied between 4 weeks and 8 years; the size of the tumour ranged from lentil to plum; all cases were histologically confirmed; no metastases were found in any of them; none of the patients was cachectic. The reaction was usually repeated; the result was invariably identical.

Since the category of "other diseases" lacked uniformity, the results yielded by it were not suited for general comparison. In 3 cases were positive reactions obtained: these patients had been operated or treated with X-rays a number of years before on account of carcinoma (uterine, laryngeal or rectal), and had no symptoms at the time of the examination. We regarded them as positive controls. The rest was divided into separate groups in accordance with the nature of the epidermal lesions.

The results are shown in tables, each of them assembling a separate group of diseases.

The group with basal-cell carcinoma shown in Table 1 included a case of superficial epithelioma with doubtful malignancy: the epithelial buds were regularly lobate, uniform and sharply marked towards the cutis; shape, staining and palisade arrangement of the cells were normal; no polymorphism or mitoses were observable; the CsTR was negative. Likewise questionable is the classification of Queyrat's erythroplasia which is regarded by many authors as precarcinosis. Keratoacanthoma, on the other hand, is often benign and heals spontaneously; only 43.9 per cent of such cases were observed by VENKEI and SUGÁR to develop into spinocellular carcinoma. Among our 3 cases of keratoacanthoma there was incipient spinocellular proliferation in one case only; another case seemed to have already turned into a prickle-cell tumour.

Table 1

Cases of carcinoma

Type	Number of cases	Positive	Negative
Basocellular	26	21	5
Spinocellular	11	4	7
Intraepithelial (Jadassohn—Borst)	1	—	1
Bowen	5	3	2
Non-differentiated carcinoma in lupo	3	1	2
Non-differentiated carcinoma of penis	2	2	—
Erythroplasia Queyrat	1	—	1
Keratoacanthoma	3	3	—
Total	52	34	18

A comparison of the clinical data with the results of the CsTR makes it evident that positivity did not depend on the duration of the tumours' development, their size or the degree of their malignancy. Most of the positive tumours were of the size of a pea or a bean and some of them were not older than 3 to 8 weeks, while one of the serologically negative tumours was 30 years old and had the size of a child's palm; the negativity in these cases might be attributed to a relative benignancy. As regards duration of positivity, there seems to be no hard and fast rule: a patient yielded a positive reaction 8 years after the surgical removal of the basal-cell tumour, while in another case the CsTR became negative 6 months after the operation.

To sum up: the proportion of positive and negative reactions varied from disease to disease; the CsTR was positive in 84 per cent of the cases of basal-cell epithelioma and in 34.4 per cent of those with spinocellular epithelioma as also 3 out of 5 cases of Bowen's disease and non-differentiated carcinoma, whereas every case of keratoacanthoma gave a positive reaction.

The incidence of positive reactions in the whole group shown in Table 2 amounted to 53 per cent. The incidence varied from category to category. Worthy of note is the fact that all cases of senile keratosis gave a positive reaction although no histological sign of carcinomatous degeneration was observed in any of them. In our case of leukoplakia there was advanced acanthosis extending deep into the cutis; inflammatory infiltration, oedema, swelling and pale staining of the basal cells at certain spots pointed to cellular disturbance without pronounced malignancy. In spite of the small number of the examined cases of chronic X-ray ulcer — such cases may be regarded as precancerous — it is worthy of attention that both gave negative reactions.

Table 2

Other malignant skin tumours and precarcinomatoses

Disease	Number of cases	Positive	Negative
Kaposi's sarcoma	8	3	5
Mycosis fungoides	1	—	1
Leukaemia cutis	1	1	—
Melanosarcoma	1	1	—
Leukoplakia labii	1	1	—
Keratosis senilis	3	3	—
X-ray skin with chronic X-ray ulcer	2	—	2
Total	17	9	8

Likewise negative was the serum of a patient who was suffering from histologically verified multiple X-ray cancer. The cases of Kaposi's sarcoma showed no parallelism in the positivity of the reaction and the extent, duration and ulceration of the process, special features of the histological structure will be discussed later.

Table 3

Benign tumours and miscellaneous skin diseases

	Number of cases	Positive	Negative
Tumours			
Epithelioma adenoides cysticum	2	0	2
Atheroma inflammatum	1	1	0
Fibroma	5	0	5
Neurofibromatosis	1	1	0
Xanthoma disseminatum	1	0	1
Multiple haemangiomata	1	1	0
Condyloma acuminatum	1	0	1
Naevus pigmentosus	4	2	2
Verruca senilis	2	0	2
Acrodermatitis atrophicans, with juxtaarticular node	1	0	1
Tuberculosis cutis			
luposa	7	1	6
ulcerosa	14	6	8
colliquativa	1	1	0

Table 3 continued

	Number of cases	Positive	Negative
verrucosa	1	1	0
papulonecrotica	2	0	2
miliaris faciei	1	0	1
indurativa Bazin	1	0	1
Sarcoid Darrier—Roussy	1	0	1
Cheilitis glandularis	1	0	1
Eczema chronicum	7	2	5
Neuroderma	6	1	5
Pyoderma	2	0	2
Acne conglobata	1	1	0
Seborrhoea capitis	2	0	2
Lichen ruber planus	1	0	1
Lichen corneus hypertrophicus	1	0	1
Induratio penis plastica	2	0	2
Vitiligo	1	0	1
Chloasma	1	0	1
Dysidrosis	3	0	3
Lichenoid purpura Gougerot—Blum	1	0	1
Acne rosacea, rhinophyma	1	0	1
Scleroderma	5	0	5
Acrosclerosis	1	0	1
Hydroa aestivalis	1	0	1
Ulcus cruris varicosum	5	1	4
Status varicosus	2	0	2
Ulcus trophicum (poliomyelitis)	1	0	1
Lupus erythematosus chronicus	2	0	2
Pityriasis rosea	1	0	1
Dermatitis herpetiformis	1	0	1
Pemphigus vulgaris	5	1	4
No skin disease	3	0	3
Total	104	20	84

The cases assembled in Table 3 were regarded as controls.

The incidence of positivity for the whole control group tabulated in Table 3 was 19.2 per cent, considerably less than in the preceding groups; it is, nevertheless, almost the double of what CSABA and TÖRŐ ascertained in their non-cancerous material (12.8 per cent). The difference could not be

due to lipemia as no such sera were involved in the reactions; there was but a single case of xanthomatosis and the reaction was negative. We have no data regarding cholelithiasis. The incidence of positivity was approximately the same for tumorous and inflammatory diseases. There were four cases of naevus pigmentosus in the category of tumours; two of them gave a positive reaction, and it is noteworthy that neither of these positive cases showed any symptom of malignant proliferation either clinically or histologically. Among the inflammatory processes the tbc cutis ulcerosa showed a high incidence of positivity which was the reason of our having examined a greater number of such cases. On the other hand, the serum of patients suffering from non-ulcerative lupus was positive only exceptionally, which makes us think that a certain correlation may exist between positivity and ulceration. We were inclined to suppose that the positivity of the CsTR in these cases was due to the formation of lupus carcinoma; since, however, no signs thereof were detected histologically and since, further, adequate antituberculosis therapy (INH; PAS; also streptomycin) had proved successful in these cases, the possibility of lupus carcinoma had to be excluded. Although the number of our cases of other forms of skin tuberculosis was not sufficient to justify general conclusions, it is worth mentioning that those which presented a picture of colliquation gave often positive, and those of a proliferative character mostly negative reactions. It is — in any case — evident that the frequent positivity of ulcerative lupus cases, as observed in our experiments, is not in harmony with the statement of CSABA and TÖRŐ that tuberculous conditions are rarely positive; this contradiction seems to point to the existence of specific factors involved in this process.

The interesting feature of our single case of crural ulcer was that a number of ulcers had healed with the exception of two; these continued to proliferate and formed tumour-like growths, which, however, histological analysis revealed as non-tumorous. There was much Schiff-positive material in the granulation, while only a few small well-defined spots of acid mucopolysaccharides and no mast cells.

The control group does not include 14 patients who had previously been treated with corticosteroids; after such treatment the CsTR seems to be very frequently positive. For instance, out of 8 pemphigus cases 7 gave a positive reaction. Considering that of our untreated pemphigus cases only one was positive it seems to be obvious that corticosteroids promote positivity. The effect may be explained by the theory that the mast cells are damaged by corticoids which would be in harmony with the observation made by CAVALLERO and BRACCINI that in the connective tissue of rats treated with cortisone the number of mast cells and the amount of hyaluronic acid are decreased. The role of hyaluronic acid in the pathomechanism of pemphigus has not been fully elucidated; it was in 14 cases out of a total of 30 that

FÖLDVÁRI and NÉKÁM observed a great number of mast cells, while only in 3 cases did they find pronounced metachromasia. Corticosteroid treatment might facilitate the breakdown of mast cells and their decomposition products might promote the formation of antibodies. In any case, during corticosteroid therapy, the CsTR cannot be used for diagnostic purposes.

Separately tabulated are those diseases in which the behaviour of the CsTR may throw some light on the theoretical foundation of the reaction so as to obtain fresh data for a further elucidation of the reaction and the interpretation of certain pathological phenomena. We are referring in the first line to urticaria pigmentosa that is histologically characterized by mast cell infiltration, and clinically by urtication due to histamine liberation by rubbing. Recently several authors have mentioned also heparin as a factor involved. ASBOE-HANSEN demonstrated the presence of hyaluronic acid and mast cells in cases of circumscribed myxoedema and pointed to inner secretory correlations, while — as regards Buschke's scleroedema — FREUND was the first to demonstrate the presence of a characteristic metachromatic mucoid substance between connective tissue and muscle fibres, as also an abundance of mast cells. The mucoid substance in question proved to be hyaluronic acid (BRAUN-FALCO). While we were able to examine 11 patients with urticaria pigmentosa, the other two diseases being less frequent, the number of cases examined was accordingly low.

Table 4

	Number of cases	Positive	Negative
Urticaria pigmentosa	11	11	—
Myxoedema circumscriptum	1	1	—
Scleroedema adultorum	2	2	—

The results in Table 4 were exactly those we had expected. It should be noted that, although we repeated the reactions several times, urticaria pigmentosa gave invariably strong positive reactions independent of the extent of the disease; a weakening of the CsTR or its negativity could be induced only by artificial intervention, *i. e.* rubbing. (A detailed account of our experiments concerning urticaria pigmentosa forms the subject of a separate communication). That the reaction was invariably positive must be regarded as a proof of the fundamental principle of the theory on which the CsTR is based. We failed in the course of our own urticaria experiments to detect either an increased amount of hyaluronic acid or a proliferation of connective tissue in the area of mast-cell infiltrations; this seems to indicate very clearly that hyaluronic acid is not involved in the formation of

precipitating immune substances and that this is induced either by heparin which is continuously released by the mast cells or by a derivate of heparin. The positivity of the reaction furnishes evidence to show that not merely local, morphologically ascertainable but also immuno-biological factors must play a part in the process; to a certain extent, it further supports the concept that — although urticaria pigmentosa is in fact no urticaria but a mast-cell naevus — it nevertheless has a certain allergic character which throws new light on KRITCHEVSKY's successful experiments. Also, it enables us to appreciate the bullous (KONRAD and WINKLER) or late papular reaction which is regarded by MELCZER as a sign of pathergic hypersensitivity.

Likewise as a proof of the soundness of the CsTR's theoretical foundation must be regarded the fact that the result was positive in our case of circumscribed myxoedema and in our two cases of Buschke's scleroedema. An increase in the amount of hyaluronic acid and in the number of mast cells are characteristic features of both diseases.

We think that our experience with the three diseases covered by Table 4 should be regarded as a striking confirmation of the theory of CSABA and TÖRŐ. There are, nevertheless, many new problems that arise in connection with processes in which results are not so uniform and correlations not as simple as in the above-discussed cases. Why does one and the same disease give a positive reaction in one and a negative reaction in another case? Why does the percentage of positivity vary from one type of epithelioma to the other? Is there any correlation between the duration, size and malignancy of the tumours, on the one hand, and the positive or negative result of the reaction, on the other? If it is true that when the reaction turns out positive it is due to the fact that the proliferating malignant tumour cells penetrate through the normal barrier of heparin and hyaluronic acid and that the formation of antibodies is then started by the depolymerizates thus formed, why do we occasionally — or even as frequently, as in the case of malignant tumours — obtain positive reactions in processes with an utterly different mechanism? What is it that upsets the physiological equilibrium in such cases?

As it was in connection with skin tumours that we were faced with a good many contradictions, and as the difference between the high incidence of positive reactions in cases of basal-cell tumour and the low incidence in those of a spinocellular tumour was especially conspicuous — a phenomenon possibly due to the different stromal reactions of the two types of tumour — we attempted to find some connection between the histological structure of the peritumoral tissues and the result of the CsTR. We made comparative estimations with a view to determining the demarcation of the tumours or their penetration into the surrounding tissue, the amount and site of hyaluronic acid, the number, position, shape and granulation of the mast cells,

the free granules, as also the presence and extent of the inflammatory infiltration and oedema. In order to eliminate possible subjective elements in assessing our results, we simultaneously performed blank experiments, *i. e.* such made in ignorance of the serological results. We were, of course, quite aware that this method was not entirely reliable, since there exist many factors which may effect the morphological picture. For instance, size and granulation of the mast cells tend to change according to the phase of their glandlike function so that their possible absence may be the very indication of intensive activity, evacuation and consequent disintegration; too, the excision itself, together with the preceding local anaesthesia (BEARE) and the subsequent fixation and staining (DEVITT, SAMUELS, PIROZYNSKI and WEBSTER) may give rise to distortion. We therefore tried to determine in the first place their number and their relationship with the collagenous fibres. It was from the same angle that we examined all other cases in which seroreactions were either uniformly negative, uniformly positive, or incidentally positive. We examined at least 3 sections in each case because the distribution of the factors to be determined is frequently uneven so that they may be absent or scanty in one specimen and abundant in the next.

We present in the following a summary of our histological studies.

Epithelioma. The outcome of the CsTR in cases of epithelioma does not depend on the extent of tumorous penetration. It is rather determined by the nature of the tumour: widespread spinocellular carcinomas usually gave negative reactions, while certain fairly circumscribed ones gave positive reactions. The opposite was the case with basal-cell tumours: most (75 per cent) of the sharply defined, solid tumours were positive. Worthy of note is the fact that we saw no penetration into the surrounding tissues in a case of a 30 year-old seronegative epithelioma planum superficiale cicatrisans, in two cases of seropositive Bowen's disease, in three cases of keratoacanthoma and in three cases of seropositive senile keratosis. The last-named three cases were especially interesting, for — as a rule — carcinomas developing from these tumours have a spinocellular character, and it is just in the malignant phase that the reaction is usually negative. It is highly improbable that precancerous positivity should turn into negativity during the process of cancerous growth. That, on the other hand, the CsTR was positive in our case of labial leukoplakia was quite in accordance with the histological analysis which revealed a certain structural disturbance of the cells at a given point and an inflammatory infiltration underneath. In general, we discovered no connection between peritumoral inflammation and the result of the reaction, although the usual inflammatory reaction was entirely absent in two negative cases of basal-cell epithelioma.

As regards fibrous reaction, our observations were in perfect agreement with those mentioned in the introductory part of this paper. A considerable

accumulation of the collagenous fibres around the tumour nests, their thickening and their frequently pronounced capsular arrangement were present in the overwhelming majority of the basal-cell tumours (in 23 out of a total of 26); it was only in 3 negative cases that the development of new fibres seemed to be scanty or altogether invisible. Again, in our fourth case we saw no fibrous reaction and positive CsTR, while in two cases there was a strong fibrous reaction and negative CsTR. Around spinocellular carcinomas the fibrous reaction was less pronounced, but we saw two exceptions with marked fibrous reaction, one of which was CsTR positive and the other negative. We observed no fibrous reaction in any of the CsTR positive cases of Bowen's disease, keratoacanthoma and senile keratosis, but encountered it in those two cases of keratoacanthoma which had developed into spinocellular carcinoma.

All basal-cell tumours revealed an increased amount of acid mucopolysaccharides; the increase was especially marked in 12 cases. On the other hand, out of 11 cases of spinocellular carcinoma it was only in four that there was some slight metachromasia; two of these cases were CsTR negative. No metachromasia could be demonstrated in any of the CsTR positive cases of keratoacanthoma, keratosis senilis and Bowen's disease. Though in general a parallelism seems to exist between fibrous reaction and the degree of metachromasia. Certain cases deviated from this rule; metachromasia, for example, was fairly marked beneath the carcinoma developing from leukoplakia although connective tissue fibres were neither increased in number nor thickened. Our impression was that in this case the primary phenomenon had really been the increased appearance of mucopolysaccharides and the formation of fibres in consequence. A similar interpretation may apply to the fact that not even traces of acid mucopolysaccharides were present in a case of melanosarcoma that had developed from a blue naevus, although, apart from spindle-shaped pigment cells, the presence of thick, almost homogenized bundles of connective tissue fibres is a characteristic feature of tumours of this type. It is obvious that the growth of collagenous fibres is already accomplished in tumours of the naevus type, while it is a continuous process in the surroundings of malignant epithelial tumours. It is at any rate undeniable that, as regards epithelioma and as yet non-tumorous epithelial hyperplasia, we failed to find a regular correlation between fibrous reaction and accumulation of hyaluronic acid on the one hand and the positivity of the CsTR on the other, however much the three phenomena are in statistical agreement as regards the groups of basal-cell and prickle-cell tumours.

Results concerning mast cells were similar to those described above. While they abounded in the vicinity of basal-cell epitheliomas, especially around the tumour-cell nests, only a few, mostly degenerated mast cells with but slight granulation were seen around spinocellular epitheliomas; the num-

ber of mast cells was, as a rule, proportional to the growth of fibres and the amount of mucopolysaccharides, but sometimes great amount occurred of the latter and no ± or hardly any — mast cells. In CsTR positive cases of Bowen's disease we observed, on the other hand, a great number of mast cells without fibrous reaction or the accumulation of hyaluronic acid.

We tried to establish a correlation between the outcome of the CsTR and the number of mast cells but did not succeed: we found just a few, degenerated mast cells in a negative case of basal cell epithelioma and some more such cells in two cases of CsTR positive spinocellular epithelioma. There were very few mast cells in the other two cases of spinocellular tumour and in those of keratoacanthoma, while a great number of mast cells was present beneath the verrucae seniles, fibromas and pigmented naevi giving a negative CsTR. Therefore the number of mast cells in itself does not seem to determine the result of the CsTR.

Considering the striking difference between the low incidence of negative results in lupus vulgaris and the high incidence of positivity in tuberculosis exulcerativa, we examined these cases histologically. Since they are characterized by the formation of granulation tissue, it is not quite easy to ascertain fibrous reaction. No or hardly any hyaluronic acid was found in either of the conditions; the number of mast cells was equally high in the positive and the negative cases alike, and there was a positive case in which only occasionally was a mast cell to be seen.

As against these partly contradictory findings, we obtained very interesting data in Kaposi's sarcoma. All positive cases revealed a great accumulation of hyaluronic acid, as also numerous mast cells around the abundantly produced thin-walled capillaries. The number of newly-formed capillaries was considerably less and their walls considerably thicker in the CsTR negative cases; metachromasia was rare and occurred only around some thin-walled capillaries; the number of mast cells was very low. We seem therefore justified in concluding to the existence of a direct relation between the outcome of the CsTR and the site and increase of hyaluronic acid; the latter, in their turn, are determined by the number and especially the developmental degree of the tumorously growing capillaries, one of the factors of the variable and complex tissue structure of Kaposi's sarcoma.

Our experimental results have convinced us that the humoral, immunobiological process which manifests itself in the result of the CsTR of the four diseases under review (urticaria pigmentosa, Buschke's scleroedema, circumscribed myxoedema and Kaposi's sarcoma) is in harmony with the histological features. It remains, however, to elucidate a number of details.

Summary

CSABA and TÖRŐ's agar binding reaction (CsTR) has been performed in 201 cases of skin disease; the result was compared to the histologic findings.

1. Of 52 cases of malignant epithelioma, 34 (65.4 per cent) were positive. Grouped according to types the percentage of positive reactions was 84 per cent in cases of basal-cell epithelioma; 34.4 per cent in spinocellular epithelioma; in 3 out of 5 cases of Bowen's disease and of non-differentiated cancers too; in 3 cases each of keratoacanthoma and non-cancerous keratosis senilis; 53 per cent in other kinds of malignant tumours and precarcinomatous conditions; 19.2 per cent in various benign tumours and inflammatory processes, especially ulcerative skin tuberculosis. A high incidence of positivity occurred during corticosteroid therapy; 7 out of 8 pemphigus cases so treated were positive as against 1 out of 5 untreated cases.

2. The incidence of positivity was different between basal-cell and prickle-cell epitheliomas; this may have been due to the more intense stromal reaction, the greater number of mast cells and the accumulation of hyaluronic acid in the first-named group, although histology yielded no clue to the cause of the discrepancy in some cases, and was in many respects contradictory.

3. No correlation was found to exist between the positivity of the reaction, on the one hand, and the malignancy, size, extension and penetration of the tumours, on the other.

4. The results have substantiated the theory on which the reaction is based. In spite of this the CsTR is not suited for diagnosis of malignant skin tumours, and cannot replace clinical diagnostics, as already stated by CSABA and TÖRŐ.

5. The reaction was positive in 11 cases of urticaria pigmentosa, in 2 cases of Buschke's scleroedema adultorum and in 1 case of circumscribed myxoedema. Histological changes in these cases were in agreement with the outcome of the reaction. In Kaposi's sarcoma CsTR positivity might be determined by the increased number of mast cells and the increased amount of hyaluronic acid around the freshly-formed thin-walled capillaries.

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ИССЛЕДОВАНИЯ РЕАКЦИИ СВЯЗЫВАНИЯ АГАРА ПРИ КОЖНЫХ БОЛЕЗНЯХ

Э. ЛИБНЕР, ДЬ. ТЕМЕШВАРИ, Ю. ЛЕНДЬЕЛ и Й. АНДЬАЛ

Серологическое и гистологическое исследование 201 кожного больного.

1. Из 52 случаев злокачественного рака кожи 34 давали положительную реакцию (65,4%). При разбивке по отдельным типам: 84% исследованных случаев базоцеллюлярной эпителиомы, 34,4% случаев спиноцеллюлярного рака, 60% случаев болезни Боуэна и недифференцированного рака, как и все случаи кератоакантомы и ракоподобно не перерожденных старческих кератодермий оказались положительными. В группе прочих злокачественных опухолей и предраковых заболеваний положительная реакция получилась в 53% случаев, в группе различных доброкачественных опухолей и воспалительных процессов — в 12,2% случаев, причем в последней группе сравнительно часто при язвенной форме туберкулеза кожи. При лечении кортикостероидами соотношение положительных реакций оказалось также высоким: в 7 из 8 леченных случаев получа-

лась положительная реакция, в то время как она была выявлена в 5 случаях нелеченных больных только в 1 случае.

2. Разницу в соотношении положительности реакций между группами базо- и спиноцеллюлярных кожных раков в общем можно объяснить большей реакцией стромы, размножением тучных клеток и гиалуроновой кислоты, однако, в первой группе, гистологическая картина отдельных случаев во многих отношениях противоречива и не выясняет данных отклонений.

3. Нельзя установить связи между положительностью реакций и злокачественностью, величиной, размером и проникании опухолей.

4. Исследования доказывают правильность теоретической основы реакции. Однако, данный метод все же не оказывается подходящим для практического диагностицирования злокачественных опухолей кожи, и не может заместить клинического диагноза, как это в отношении опухолей кожи также было установлено исследователями *Чаба* и *Тёрё*.

5. В 11 случаях **urticaria pigmentosa**, 2 случаях **scleroedema adultorum Buschke** и 1 случае **myxoedema circumscriptum** получалась 100%-ая положительная реакция. В этих трех картинах болезни тканевые изменения также теоретически находятся в полном согласии с гуморальным процессом, проявляющемся в реакции; при **Sarcoma haemorrhagicum (Kaposi)** кажется, что положительная реакция связана с размножением тучных клеток и гиалуроновой кислоты вокруг новообразованных тонкостенных капилляров.

DIE AGARBINDUNGSREAKTION BEI HAUTKRANKEN

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Bei 201 Hautkranken wurde die Agarbindungsreaktion ausgeführt und auch histologische Untersuchung wurde vorgenommen.

1. 34 von 52 Fällen maligner Epitheliome ergaben eine positive Reaktion (65,4%). Nach Typen geteilt ergaben 84% der basozellulären Epitheliomen, 34,4% der spinozellulären Epitheliomen, 60% der untersuchten Fälle von Bowen-Krankheit und nichtdifferenzierter Krebserkrankungen und alle utersuchten Fälle von Keratoakanthom und nicht krebsartig entartetem Keratosis senilis eine positive Reaktion. In der Gruppe der übrigen malignen Geschwülste und präkanzerösen Erkrankungen wurde eine positive Reaktion bei 53%, in den von gutartigen Geschwülsten und entzündlichen Prozessen bei 19,2% ermittelt, in der letzteren Gruppe besonders ulzerierter Hauttuberkulose. Während der Behandlung mit Kortikosteroiden waren die positiven Reaktionen häufig: 7 von 8 behandelten Pemphigusfällen ergaben eine positive Reaktion, während aus 5 unbehandelten Fällen nur 1 Fall positiv ausfiel.

2. Die häufigere Positivität der basozellulären Epitheliome im Vergleich zu den spinozellulären Epitheliomen kann mit der intensiveren Stromareaktion, der Vermehrung der Mastzellen und der Hyaluronsäure bei den ersteren erklärt werden, doch ist das histologische Bild in vieler Beziehung widersprechend.

3. Zwischen der Positivität der Reaktion und der Bösartigkeit, Ausdehnung, sowie Penetration der Geschwülste konnte kein Zusammenhang festgestellt werden.

4. Die Untersuchungen bestätigen die Richtigkeit der theoretischen Grundlage der Reaktion. Sie scheint jedoch für die Diagnose von malignen Hautgeschwülsten nicht geeignet zu sein und kann die klinische Diagnose nicht ersetzen, wie dies in bezug auf Hautgeschwülste auch von CSABA und TÖRŐ festgestellt wurde.

5. Bei 11 Fällen von Urticaria pigmentosa, 2 von Scleroedema adultorum Buschke und 1 Fall von umschriebenem Myxödem fiel die Reaktion ausnahmslos positiv aus. — Bei diesen drei Krankheitsbildern zeigten auch die Gewebsveränderungen eine Übereinstimmung mit dem in der Reaktion sich manifestierenden humoralen Prozess. Bei Kaposischer Sarkomatose scheint die Positivität der Reaktion mit den in der Umgebung der neugebildeten dünnwandigen Kapillaren sich vermehrenden Mastzellen und der Hyaluronsäure zusammenzuhängen.

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