ACTA MORPHOLOGICA

ACADEMIAE SCIENTIARUM HUNGARICAE

REDIGIT
I. TÖRŐ

SUPPLEMENTUM VIII

AKADÉMIAI KIADÓ
BUDAPEST
1959

PROCEEDINGS OF THE ANNUAL MEETING OF HUNGARIAN PATHOLOGISTS AND ANATOMISTS

Hévíz, 1958

PLENARY SESSION

Pathology of the Rheumatic Diseases

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Pathology of the Rheumatic Diseases

Recent advance in research on connective tissue has made it possible to study the morphological changes occurring in rheumatic conditions with respect to connective tissue elements, especially to the intercellular matter (fibres and the so-called amorphous ground substance). The most important task now is to integrate the data obtained in recent years from the point of view of rheumatism.

The discovery of the Aschoff bodies represented a significant advance in the pathology of rheumatic disease. Then the allergy doctrine made it possible to approach the problem of pathogenesis from a new angle. KLINGE (was the author to recognize the remarkable similarity of the morphological changes occurring in allergy and rheumatic conditions. The studies of HENCH and KENDALL directed attention to the pituitary-adrenal system, which is also in the centre of the so-called adaptation theory of SELYE, according to which an increased output of mineralocorticoid hormones would be primarily responsible for the development of connective tissue changes. SAYERS suggested that rheumatism would be due to a primary insufficiency of tissues against hormonal actions. The hormonal theories focussed increased attention on the role of the nervous system and soon it was claimed that a major group of rheumatic conditions, the so-called rheumatoid arthritis (primary chronic polyarthritis) was due to a neuro-endocrine disorder, the course and localization of which is determined by the autonomic nervous system. The emphasis shifted from the precipitating factor to the response of the organism.

The various views on pathogenesis agree in attributing a significant role to the mesenchyma in the development and course of the disease. This means a close connection with the so-called hormonal theory, because hormones play an important role in the physiological or pathological function of connective tissue. Beside the hormones, the enzymes of connective tissue and of plasma seem to have a significant part to play. The enzymic or dysfermentative

theory of the pathogenesis of rheumatism is based on an imbalance claimed to exist between hyaluronidase and hyaluronic acid. Haemolytic streptococci, these organisms so important in rheumatic conditions, are definitely hyaluronidase producers. Other bacterial enzymes may also be at play. Almost all of the bacteria which may be involved in the pathogenesis of rheumatism all contain amino acid decarboxylase, first of all histidine decarboxylase, which in certain conditions converts histidine to histamine. In acute articular inflammations the serum has been proved to exert an increased histidine decarboxylase activity. In cultures, histidine decarboxylase causes a release of mucopolysaccharides from connective tissue linkages. If the loss of mucopolysaccharides amounts to about 10 per cent, the connective tissue fibres swell and lose their normal shape and a loss amounting to 20 to 25 per cent converts collagen to a homogeneous mass.

Recent information concerning the physical, chemical and histological properties of connective tissue has opened up a new chapter of research on mesenchymal diseases. The fundamental statements made by KLEMPERER et al. have placed into the focus of interest the changes in the intercellular matter of connective tissue, with the result that a common pathogenetical view has been developed for a variety of conditions which earlier had been thought to be heterogeneous. In view of the similarity of the changes in the ground substance of connective tissue, these conditions have been denoted by the common term of collagenosis. The most characteristic representative of the group is rheumatic polyarthritis.

Summing up, none of the theories has offered a full explanation for the aetio-morpho- and pathogenesis of rheumatic diseases. It appears that various factors may start the process, which is determined by constitutional dispositional conditions, individual responsiveness, in at least the same measure as by certain, often overestimated, exogenous factors.

In the definition of the concept of rheumatic diseases we find two extremes viz. 1. the pathological-anatomical definition based on the presence of Aschoff bodies or of allergic changes in tissues; and 2. the clinical definition, which is based exclusively on symptoms and signs. The International League against Rheumatism has on its records more than 60 different classifications. Considering that in every case the emphasis is on mesenchymal changes, any organ or tissue of the body may be affected. A true picture of the pathology of rheumatism can be obtained exclusively by a synthetic analysis of the clinical and morbid anatomical data.

Streptococci are important factors in pathogenesis. Rheumatism is by no means a simple infectious disease and in all likelihood streptococcal infection develops in a previously sensitized organism. The streptococcal factors of particular importance are streptokinase (fibrinolysin), streptodornase (which breaks down nucleotides) and hyaluronidase. Common symptoms and signs

of an infectious disease are usually absent and repeated infection is apparently of importance. Studies in experimental rheumatism have elucidated these and other aspects of the problem.

In the rabbit, even a single experimental infection with streptococci may give rise to arthritis. ALBERTINI and GRUMBACH found endocarditis in 21.2 per cent, articular changes in 51.4 per cent and myocardial changes in 25.3 per cent of the 315 rabbits given a single intravenous injection of streptococci. These authors, rejecting the allergic theory, claim that the actual responsiveness and the virulence of the pathogen will determine the type of disease. Repeated treatment with streptococci or with toxin gives rise to perivascular infiltrations in various organs. The presence of basophilic cells is a characteristic feature. In their interesting experiments, MURPHY and SWIFT infected rabbits with streptococci containing protein M and after 3 to 20 months of observation found clinical and pathological changes resembling those usual with rheumatic disease. In contrast to ALBERTINI and GRUMBACH, they emphasize that the changes do not develop after a single injection.

According to the hypothesis of CAVELTI, a preceding streptococcal infection would liberate substances of antigenic nature from the connective tissue, and the characteristic changes would develop, after a period of latency, on the basis of the antigen-antibody reaction.

Viral infection has been suggested to be the decisive pathogenetic factor by numerous authors (PEARCE, COPEMAN, SCHLESINGER, GORDON, and others).

There are many data on sensitisation with foreign protein. The hyperergic inflammation of joints merits particular attention; it has been proved by KLINGE who succeeded in eliciting the Arthus phenomenon in joints. It is most remarkable that in sensitized animals the same changes may be elicited by non-specific effects, for instance by cold. In exhausted animals even a low dose of serum is effective and such animals show a conspicuous sensitivity. SELYE succeeded in inducing polyarthritis by excessive doses of DOCA. Cortisone prevents the development of this polyarthritis. SELYE also induced arthritis by the injection of formalin; this arthritis is intensified by DOCA and weakened by ACTH and cortisone.

Summing up, single or repeated administration of streptococci or of foreign protein produce changes which in many a feature resemble those occurring in human rheumatic disease. The same applies to certain adrenal cortical hormones. It should, however, be borne in mind that these changes either belong to the general systemic reaction (*e. g.* inflammation, mesenchymosis), or (as, for instance the fibrinoid change) are too simple by themselves to characterize some process.

Both the experimental data and human pathology show the rheumatic tissue reaction to be of an allergic-hyperergic nature. The allergic reaction

presents with serous inflammation. This may be considered allergic only when followed by changes characteristic of the so-called allergic tissue response: appearance of peculiar cellular elements, fibrinoid change, formation of granulation, then scar tissue. According to RÖSSLE, every inflammation associated with granulation develops on grounds of an allergic-hyperergic mechanism.

The visceral manifestations of serous inflammation can excellently be studied in the case of endocarditis; in this case the valves may be considered to be parts of the blood vessel system. According to BÖHMIG, interstitial oedema is the primary change, followed by endothelial damage. The fibrinous exudate arises not by a simple superposition. In a certain sense the precipitation of fibrin means that the inflammatory process has subsided and may even offer some chemical-biological protection. The exudate formed in serous inflammation is poor in cells and fibrin, but contains ample amounts of mucopolysaccharides.

The fibrinoid change, so significant among the rheumatic tissue alterations, develops on the grounds of serous inflammation. The fibrinoid is not homogeneous in structure and its morphogenesis has not been elucidated. In the course of the fibrinoid change, the collagen fibre becomes homogeneous and intensely eosinophilic; fibrin is precipitated in the interfibrillar space and ultimately also the ground substance is altered. Chemical studies showed fibrinoid to be a precipitation or coacervation of acid mucopolysaccharides and basic proteins. The fibrinoid of the rheumatic nodule contains neither proline nor hydroxyproline. This fact, together with the results of X-ray-diffraction studies, indicate that the substance does not originate from collagen. According to BUSANNY—GASPARY, fibrinoid would be (aged) fibrin, to which other substances adhere secondarily. French authors (J. DE BRUX) claim that fibrinoid is not the result of a metamorphosis of the ground substance, but arises from fibrinogen precipitated in a special medium.

The peculiar genesis of fibrinoid is reflected also by the observations made in cases of lupus erythematosus: a fibrinoid-like substance is formed when the haematoxylinophilic metabolites of nuclear protein undergo further breakdown. Such a substance has been demonstrated to occur in the lumen of blood vessels, too, and these substances might perhaps enter the interstitial space.

The divergence of opinion as to the composition and formation of fibrinoid may be explained by a misinterpretation of histochemical findings. For example, the presence of acid mucopolysaccharides in fibrinoid has been claimed to indicate that the ground substance of fibrinoid would originate from the so-called amorphous ground substance, although the collagen complex contains the same polysaccharides as those contained in the ground substance. New, pathological compounds are formed from the proteins and polysaccharides originating from desorganized collagen fibres, ground substance

and blood, and, as a result, a series of pathological changes take place, the fibre bundles are altered, pathological structures are formed (*e. g.* focal necrosis). STRUKHOV and ORLOVSKAYA have classified the connective tissue changes into four types.

ROMHÁNYI et al. have shown by polarization-submicroscopic analyses that the fibrinoids occurring in different tissues are structurally different. The fibrinoid in the placenta and goitre is pure fibrin, whereas that in connective tissue, bursae, ganglia and vascular wall is fibrin precipitated in the interfibrillar spaces of connective tissue. No fibrin has been detected in the fibrinoid present in rheumatic connective tissue or in gastric ulcers.

Thus, histochemical and submicroscopic studies on the structure of fibrinoid indicate that this substance, which when stained by simple histological techniques appears to be homogeneous actually varies in composition and for this reason cannot be accepted as a characteristic of allergic or rheumatic conditions.

The classic element of rheumatic tissue changes is the Aschoff body. The significance of this histological change has been accepted universally. More recently, MURPHY has shown in rabbit experiments that almost invariably the Aschoff bodies develop on the ground of local myocardial destruction. ALBERTINI, too, is of the opinion that the necrotic material contains not only connective tissue, but muscle as well. The myocytes of ANITCHKOV are believed to be typical histiocytes. Summing up, it may be stated that the Aschoff body is characteristic of rheumatism; the formation of granuloma is preceded by tissue damage. As to the nature of this latter the views are not uniform; it may be fibrinoid necrosis of connective tissue, primary necrosis of muscle, or both. The cellular reaction is of resorptive nature.

Chronic polyarthritis (rheumatoid arthritis) occupies a special place in rheumatology. The aetiological role of streptococci, accepted almost universally in acute rheumatism, is not of general validity in the case of rheumatoid arthritis, in which endocrine and neurological factors predominate. The term rheumatoid is a collective one in the Anglosaxon and Scandinavian literature, whereas in Germany sharp distinction is made between the primary and secondary forms of chronic polyarthritis. EDSTRÖM has suggested that rheumatic fever is a hyperergic response, chronic rheumatism is based on latent allergy and septic rheumatism is an anergic condition. ASCHOFF, GRÄFF and FAHR emphasized the difference between acute and chronic polyarthritis. KLINGE believes that primary and secondary polyarthritis belong to the same nosological group, differing only the form of appearance. According to SELYE rheumatoid arthritis is an adaptation disease. The histological changes found in this disease correspond to those occurring in chronic, nonpurulent inflammations; ultimately, the changes lead to scar formation and the joint becomes completely obliterated and deformed. Subcutaneous rheumatic nodes are also detectable.

FREUD, LEICHTENTRITT and STEINER found fibrinoid necrosis and granulation in peripheral nerves. RADNAI attached importance to necrosing arteriitis. All the other views emphasizing the role of the nervous system are lacking a firm histological basis.

It has often been claimed that acute rheumatism is practically never followed by chronic rheumatism. In the knowledge of the visceral localization and the nature of the disease, this view is hardly tenable. GROSS is of the opinion that qualitatively the same pathoanatomical changes occur in primary and secondary polyarthritis and for this reason just one kind of chronic form should be acknowledged, the one termed rheumatoid in Anglosaxon and Scandinavian literature. SCHWARTZ and SCHLOSSMANN have aroused considerable interest when by precipitation, electrophoresis, chromatography and ultracentrifugation they isolated the so-called rheumatoid factor, a macroglobulin.

Collagen diseases and rheumatism. Since it has been suggested that both rheumatic fever and rheumatoid arthritis are collagen diseases, it seems worthwhile to discuss this group of diseases. The common feature of collagenoses is the occurrence of systemic changes in the connective tissue, especially in the intercellular substance. The characteristic changes and symptoms include fibrinoid degeneration, dysproteinaemia, chronic and progressive course, involvement of stress factors in the onset and relapses of the disease, and the facts that most clinical symptoms are localized to the organs of locomotion or to the blood vessels, and that temporary benefit is derived from the use of cortisone or ACHT. All these apply to the so-called rheumatic diseases as well. PETRÁNYI, in a study on polysystemic lupus erythematosus, has illuminated the correlation between rheumatic diseases and collagenoses in a noteworthy manner. According to him, in the group of rheumatic and collagen diseases lupus erythematosus is the central syndrome, which supplies convincing data as to the pathogenetical indentity of the various pertaining conditions. As determined by an analysis of 33 cases, there are several intermediary forms and the relation between the collagen diseases can be proved not only histologically, but clinically as well. This view may shed light on the relationship between the various rheumatic syndromes (Felty's, Still's, Sjögren's), which are closely related and in which the rheumatic factor is invariably detectable.

Connective tissue and rheumatism. There is almost general agreement that changes of the connective tissue play a decisive role and that its individual and actual responsiveness practically determine the development and course of rheumatic disease. For this reason, studies on connective tissue, especially on collagen and the so-called amorphous ground substance are of great importance. The complex structure of collagen cannot be discussed here, let it suffice that even when grave changes are revealed under the usual light microscope, electron microscopy or submicroscopic examination will disclose no marked alterations, only a shift in the relation of collagen to ground substance.

The changes in the structure of connective tissue are controlled by complex mechanisms, of which the enzymic effects are the most important, first of all that of hyaluronidase, the enzyme by which hyaluric acid is depolymerized and hydrolysed. HEINLEIN and others produced oedema and arthritis by treatment with hyaluronidase. It has not been decided whether an increase of hyaluronidase activity in tissues, an inflow from plasma or a functional change of the inhibitor is responsible for them. The inhibitory factor is bound to globulin and is closely related to the function of DOCA and histamine. Little has been elucidated concerning the effect and mode of action of hyaluronidase : according to SZABÓ and MAGYAR, it increases capillary permeability.

The structure of the ground substance is most variable. GERSH observed that mild mechanical irritation of the skin already suffices to induce its depolymerization. According to GREENSPAN, in inflammatory conditions mucoid is broken down rapidly. During the first hours of inflammation the ground substance increases in volume and its depolymerization is enhanced. There is evidence to show that the mucopolysaccharides of plasma and tissue are not being formed where we find them : their site of formation is however, unknown. The correlation between the mucopolysaccharides of the ground substance and those of plasma is gaining in significance. Some authors claim that in certain diseases the increased amount of polysaccharides in the plasma originates from the ground substance, whereas others suggest that the mucopolysaccharide in the ground substance comes from blood. The blood mucopolysaccharide level has been observed to increase in rheumatic fever and rheumatoid arthritis. RICHTER has shown that the subcutaneous administration of histamine markedly affects the amount of protein-bound mucopolysaccharide in the blood. The effect of histamine is more marked in polyarthritis and rheumatic fever than in inflammatory conditions of other nature. Cortisone completely blocks the action of histamine.

Microscopic and microchemical studies on the mode of action of butazolidine have shown that in response to that drug the mast cell count and the glycoprotein level of serum increase. When injected intradermally, butazolidine causes an excessive increase of acid mucopolysaccharides, a mesenchymal cell proliferation and transformation in the area of the injection. It appears that butazolidine acts on the ground substance of connective tissue, releases acid mucopolysaccharides in direct proportion to the increase in the mast cell count of blood. The number of circulating mast cells is in relation with the increase serum of the mucopolysaccharide level.

All the above data emphasize the importance of mesenchymal tissue in the pathogenesis of rheumatism. In histological studies of rheumatic disease special attention should be devoted to both the fibres and the amorphous ground substance. It is hoped that analyses of this kind will elucidate pathognomonic features within the single morphological changes.

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The Role of Polysaccharides in Connective Tissue

Connective tissue and its polysaccharides are today in the focus of interest. One of the reasons for this is that rheumatic fever and collagen diseases are associated with pathological changes in the connective tissue. Further connective tissue, being one of the commonest kind of tissue, is directly or indirectly affected in every disease. Useful information may therefore expected from morphological and chemical studies of its basic components and the correlation between structure and function.

Connective tissue is built up of 4 principal components differing from one another both morphologically and chemically. These are the cellular matter, the various forms of collagen fibres, the elastic fibres and the ground substance. Among these it is the ground substance that contains significant quantities of polysaccharides, notably the acid mucopolysaccharides. Their role has not been fully elucidated. According to MEYER (1950), they constitute a framework or template, within which the protein may form fibres. On the other hand, PARTRIDGE (1948) is of the opinion that the single elementary components of the collagen fibre are held together by a substance displaying striation and this substance would be the acid polysaccharide.

It would be of extreme importance to establish whether or not connective tissue contains polysaccharides which are chemically and histologically different from the acid mucopolysaccharides. In general, histologists, pathologists and electronmicrographists designate as cellular polysaccharides those substances which stain metachromatically or give a positive periodic acid Schiff's (PAS) reaction. Some authors make them responsible also for argyrophilia (SCHWARZ, 1957). To the acid mucopolysaccharides belong the chondroitin sulphates A, B and C, hyaluronic acid, keratosulphate and heparin. The problem of metachromasia has been elucidated in some detail by the use of hyaluronidase, insofar as it became apparent that it is the sulphated mucopolysaccharides in the first place that show metachromasia. The enzyme hyaluronidase digests the acid mucopolyssaccharides (except chondroitin sulphate B) and this leads to a loss of metachromatic staining. This reaction is specific for the acid mucopolysaccharides. The situation is different with the PAS reaction. The fact that certain acid mucopolysaccharides (hyaluronic acid, mucoitin sulphate) are also held responsible for the positivity of the PAS reaction, has been a source of much confusion. There is ample evidence that the neutral mucopolysaccharides are also involved in the PAS positivity. The aim of the chemical research is to offer exact evidence as to the basis of histo-

logical reactions. We shall now discuss data from the literature and our own observations concerning the PAS reaction which now is being universally applied in the histology of connective tissue.

Recently, it has been shown that the connective tissue contains, beside acid mucopolysaccharides, also significant amounts of heteropolysaccharides containing no hexuronic acid and no sulphate group, *i. e.* neutral polysaccharides. It is therefore justified to ask whether polysaccharides other than the acid ones take part in the histochemical reactions. The difference in composition between acid and neutral polysaccharides is shown schematically in *Table I*. The first neutral heteropolysaccharide was detected in 1938 by HISAMURA, a Japanese scientist, in the so-called osteomucoid of bone.

Table I

Composition of Polysaccharides

Composition		
Acid mucopolysaccharides	Neutral heteropolysaccharides	
	I	II
Hexuronic acid	Hexoses	Hexoses
Hexosamine	Fucose	Hexosamine
Sulphate group		

CONSDEN (1953), as well as GLEGG, EIDINGER and LEBLOND (1953), isolated from skin, tendon, cartilage and bone such protein containing fractions which after hydrolysis were found to contain exclusively monosaccharides, *i. e.* which were different from acid mucopolysaccharides. DISCHE, DANILCZENKO and ZELMENIS (1958) proved chemically that the vitrous body and the bone contain two different types of neutral heteropolysaccharide. Interfibrillar material also contains a protein in which there is 12 per cent of carbohydrate. The latter protein greatly resembles plasma globulin, but, according to the above authors, it differs from globulin in the composition of certain structural factors. WINDRUM, KENT and EASTOE (1954) published the important finding that reticulin contained much more (4.2 per cent) polysaccharide than collagen and that this polysaccharide, lacking in both hexosamine and hexuronic acid, is different from the acid mucopolysaccharides and according to the usual terminology, is therefore a neutral polysaccharide. Since the histological difference between collagen and reticulin manifests itself partly with argyrophilia and partly with the content in PAS positive substance, in reticulin it is presumably the neutral polysaccharides which are responsible for the combination with silver and for the PAS positivity. CONSDEN, GLYNN and STANIER (1953) found that the cubital connective tissue and the rheumatic

nodes of children suffering from rheumatic fever contain more reducing sugar than the same tissue of normal subjects. This sugar contains a minimum amount of hexosamine and no hexuronic acid. Thus, neutral polysaccharides and not acid mucopolysaccharides are increased in amount.

According to the above data, neutral polysaccharides are in fact present in connective tissue. It remains, however, to be decided whether these polysaccharides are components of connective tissue or are present merely as contaminants. Contamination may originate mainly from the polysaccharides bound to serum protein. Although the careful studies of NEUBERGER et al. (1957) showed that connective tissue contains 10 to 15 times more blood protein than what would correspond to the quantity of blood vessels, it is still unclear whether this blood protein and the neutral heteropolysaccharide in it had any role in the morphogenesis, metabolism or function of connective tissue fibres. MEYER (1957) did not include the neutral polysaccharides and glycoproteins in his list of connective tissue polysaccharides, partly because well-defined compounds have not been isolated and partly because it has not been proved that the substances in question would differ from plasma proteins.

At the London symposium on connective tissue in 1956, in opposition to the histologists the chemists claimed that the polysaccharide in collagen fibres is but a contamination and the connective tissue fibre is composed exclusively of polypeptide chains built up from amino acids. In contrast with this, GRASSMANN, HOFMANN, KÜHN, HÖRMANN, ENDRES and WOLF (1937), as well as ROMHÁNYI (1958), suggest that the polysaccharides have a role to play in the alterations of fibres.

The chemists are basing their arguments mainly on the results of chemical analyses, presented in *Table II*. It was found that isolated connective

Table II

Classification and Chemical Composition of Fibres

	Amino acids %	Polysaccharides %	Lipids %
Collagen fibres	95	0.5	?
Argyrophilic fibres	86	4.5	10
Elastic fibres	96	0.3	trace

tissue fibres, elastin and collagen consist in 95 to 96 per cent of amino acids and contain only traces of polysaccharides, except for the reticular fibres which contain 4.2 per cent of polysaccharides. The chief argument put forward by the histologists is that the morphogenesis of connective tissue fibres, the process of wound healing and also the pathological processes manifest them-

selves with changes in the polysaccharide reactions, so that in whatever small a quantity they are present, these polysaccharides must play a role both in the build-up and the pathological alterations of the fibres.

In 1954, TUSTANOVSKY, ZAYDES, ORLOVSKAYA and MIKHAILOV put forward their theory according to which the collagen fibre is a multi-component, multi-phased system, composed of two kinds of collagen, *vis.* procollagen, soluble in dilute acid buffers, and collastromin, an insoluble substance. In normal conditions the two kinds form a complex, but under pathological conditions a desorganization of the collagen fibre takes place. In his studies on the collagen diseases, STRUKOV (1958) distinguished between 4 forms of intercellular connective tissue changes. On grounds of the evidence obtained, the Soviet authors suggested that the polysaccharides of the ground substance and those of the collagen complex are equally involved in the changes. From this it follows that they accept the presence of two kinds of polysaccharide in collagen tissue.

The problem cannot be solved before it has been proved that collagen tissue contains not only acid, but also neutral polysaccharides as integral parts of the fibrils and further, these play a role in the function of the fibres. These should be proved both chemically and functionally, because only a combination of the two results can be accepted as a decisive argument. In our opinion, the final proof would be to show that dissolution of the neutral polysaccharides gives rise to essential changes in the physical, physico-chemical and functional properties of the collagen fibre. We have carried out successful experiments in this respect with the enzyme collagenmucoproteinase isolated by us (BANGA, BALÓ 1956). From collagen tissue containing only traces or no acid mucopolysaccharide (for instance from mature collagen fibre of tendon) that enzyme dissolves a protein which contains a neutral heteropolysaccharide and which therefore greatly differs from the proteins containing the known acid polysaccharide. We (BANGA, 1958) have succeeded in isolating this material in a pure (70 to 100-fold) form. The pure substance is called mucoid$_2$. Chemical analysis has proved mucoid$_2$ to be different from the acid mucopolysaccharides.

In the functional studies we had started from the hypothesis that if the neutral polysaccharide belongs to the collagen fibre and is an ingredient of it than changes should take place in the properties of the fibre after the neutral polysaccharide had been eluted from it. This hypothesis proved to be valid. The polysaccharide-free fibres treated with the enzyme were different in the chemical contraction-relaxation experiment, in the hydrothermal test and in their physico-chemical properties. According to the investigations of BANGA, BALÓ and SZABÓ (1956), in 40 per cent KJ at 20° C the native collagen fibre contracts to 1/3 of its length and becomes three times thicker. This is called chemical contraction. A similar reaction is observable during hydrothermal

contraction. On the other hand, the fibre from which the mucoid$_2$ has been removed by treatment with collagen mucoproteinase merely shrinks (without increasing in thickness) in these tests. Subsequently, the fibre disintegrates into filaments and breaks. Finally, the fibre as a whole loses its double refraction and is dissolved by the imbibing fluid. Thus, treatment with the enzyme results in the formation of a fibre which has lost its stability, as it is apparent from the fact that during heat or chemical contraction it is unable to work but breaks immediately. The disintegration to fibrils takes place equally either being loaded with weight or without it.

Meanwhile, the physico-chemical properties of the fibre also change, as it is clear from its behaviour in dilute acetic acid. Whereas the untreated fibre shows some swelling in dilute acetic acid, followed by fibre formation after drying or precipitation with salt, the fibre treated with collagenmucoproteinase disintegrates in dilute acetic acid to such an extent that it is no longer possible to reconstitute a fibre from it. This means that fibre formation reaction of NAGEOTTE, used also by HUZELLA, cannot be carried out with a fibre lacking in neutral polysaccharides. From this it follows that this neutral polysaccharide is the agent which keeps the fibrils or filaments together in a certain stage of fibre formation. Thus, the enzyme dissolves a polysaccharide, which keeps the fibrils together in the collagen fibre. If it is absent from the fibre, the fibrils dissociate in acetic acid or in concentrated salt solutions.

This neutral heteropolysaccharide is bound to protein in the collagen fibre. According to the amino acid analysis of the purest preparations, the protein in question is apparently different from the protein of collagen, but this requires further studies. On the basis of its chemical properties it can be considered a neutral heteropolysaccharide. It has been shown that this neutral polysaccharide is responsible for the periodic acid Schiff reaction of collagen and reticulin fibres. If this substance is dissolved from the fibres by treatment with collagenmucoproteinase, the periodic acid Schiff reaction disappears almost completely. Collagen fibre isolated from the tail tendon of the rat, or smears of broken-up Achilles tendon are most suitable for demonstrating this. Both react strongly with the PAS reagent if untreated and show hardly any reaction after treatment with collagenmucoproteinase.

Thus, by means of the enzyme collagenmucoproteinase it could be proved that the neutral heteropolysaccharides, the existence of which has been suggested but not proved by other authors are integral parts of the connective tissue fibre. They are present in the collagen fibre not as contaminants because on this lysis the properties of collagen fibre change.

On the basis of its chemical analysis we consider this neutral heteropolysaccharide to be a mucoid and call it mucoid$_2$, because the bond between the polysaccharide and protein is very firm. We distinguish it from mucoid$_1$ (BANGA, 1953), which is liberated from collagen tissue on hydrothermal

treatment. Mucoid$_2$ is responsible for the periodic acid Schiff reaction of isolated collagen fibres, whereas mucoid$_1$ appears to be responsible for the binding of silver. Unfortunately, the chemical basis of the latter reaction is still unclear and for this reason we can say no more about it.

It is thus obvious that investigations into the nature of neutral polysaccharides are still in an elementary stage. The greatest difficulty is that these agents are present in quantities so small that they cannot be analysed chemically. The only way to approach them is by the use of specific enzymes. In contrast with their minute quantities, they are important compounds and it is not too farfetched to claim that the clarification of their properties will stimulate further research in the field of rheumatism.

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Relation of Symptoms and Pathology in Rheumatic Disease

In rheumatic complaints, the leading symptom is almost unanimously pain, accompanied by locomotor disturbances, muscular atrophy, and finally by grave deformations.

In the present paper, exclusively one of these four symptoms, — namely pain, — shall be discussed at some length.

Physiology teaches us that pain can be elicited by practically any stimulus, although the energy involved therein must be considerably superior to that which brings about tactile or thermal sensations. Impulses encountered in everyday life need hardly be enlarged upon : pressure, tearing, pricking, as well as heat or cold are the mechanical impulses, whereas chemical stimuli include hyper- or hypotonic solutions, acids, bases, with their consequent pH alterations, and finally electrical impulses.

The question which has claimed our attention is the genesis of the so-called "rheumatic" pain, *i. e.* the chemical or mechanical stimuli responsible for the above, under given physiological or pathological conditions. This factor would be the missing link between the histological and histochemical alterations observed in the diseased area and the symptoms recorded by the patient.

Chemical factors

According to JENDRASSIK (1955), potassium is the commonest substance occurring under physiological conditions which may be held responsible for pain; the potassium set free by cellular destruction and behaving henceforward

as an extracellular substance may stimulate the neural fibre-endings with a consequent sensation of pain. It is a matter for further speculation how far this process applies to cells destroyed by disease. Anoxaemia certainly does induce painful sensations — a fact corroborated by numerous clinical observations. The question remains, whether oxygen deficiency and subsequent changes in pH are by themselves a sufficient cause of pain, or whether the accumulation of breakdown-products due to poor oxygenation is the immediate painful factor. — JENDRASSIK states that, in his experience, histamin proved a potent stimulant, followed — however — by itching rather than pain. We are indebted to LEWIS for his well-known concept of the "P-factor", including the above pain-inducing agents. Unfortunately, we are still at a loss in regard to the full meaning covered by this heading.

Mechanical factors

Mechanical factors are undoubtedly liable to produce pain and are commonly met with in everyday life. Pain upon unwonted traction of internal organs corresponds to the extension of the smooth musculature and can be explained by the attending cramps. Recent experiments tend to prove that the extracellular space is increased in rheumatoid arthritis. Although the concomitant distension of connective tissue can hardly give rise to pain, it may well account for eventual tenderness.

Pressure is another frequent stimulus bringing about pain. The question seems to be, once more, whether pain is set off by pressure *per se*, in a purely mechanical way, or as a secondary phenomenon due to circulatory stasis, — hence, to anoxia?

Electrical factors

Electrical factors are most probably responsible for the rheumatic pains recorded by patients upon changes of atmospheric conditions. To date, we have no adequate explanation for the correlation of changes in atmospheric ionization and incidence of pain. Hypothetically, the rheumatic nodules, with their poorly vascularized structure, might be subject to pain, which brings us back to the concept of ischaemia.

Thermal factors

Cold, as a determining factor of rheumatic pain is widely recognized, and acts very probably by way of vascular spasms within the affected tissues, swinging back once more to anoxia as the causal agent. A different — and possibly more interesting — aspect of the matter lies in the protracted pathogenic effect of cold, as everyone with an experience of delayed war-time injuries due to exposure to cold (not frost-bite) will have observed.

After this brief summary, I shall proceed to discuss the different gross and histologic changes which may be involved in the genesis of pain.

Serous inflammation induces violent pain whenever it takes place in a closed area where mechanical pressure is bound to occur. We are, however, justified in accepting the hypothesis that serous inflammation acts as a chemical stimulus upon the neural fibre-endings. The histochemical basis of this painful reaction is unknown. It is a current bedside experience that a serous exsudative process is painful in its initial stage and gradually brings about an adaptation of the affected organs to meet the needs of the augmented fluid content. A new onrush causes renewed pain, though the volume of serous exsudate does not necessarily show a further increase. An other duly observed fact shows that tuberculous inflammation is much less painful than the corresponding rheumatic process.

The rheumatic granulome — or KLINGES interstitial microgranulome, which appears in the myocardium as Aschoff's node, — as well as the large subcutaneous rheumatic nodules of severe rheumatoid arthritis are probably as many sources of pain. According to clinical experiences, Meynet's nodules are tender only upon palpation; nonetheless, muscular pain, electively located around the tendon-heads, is a frequent complaint of patients with rheumatoid arthritis. It is hardly possible to assess whether the onset of pain corresponds to the stage of fibrinoid degeneration or to that of beginning granulation.

FREUND, LEICHTENTRITT and STEINER found round cell infiltration of the perineural tissues in rheumatoid arthritis. These findings must, however, be considered carefully as these nodules probably cause pain by the pressure exerted upon neural fibres.

The *fibrous rheumatic nodule*, — this terminal form of the granulome, is a potential causative factor of pain. It seems reasonable to assume that this poorly vascularized scar tissue may induce pain when innervation is present.

Fibrinoid degeneration, as a painful factor, strikes us as the major problem of its kind. According to KISS's latest observations, collagenous fibres are embedded in a mesh of sympathetic nerve-endings. The subsequent hypothesis, that the groundsubstance represents a receptor for painful sensations, and that histochemical alterations taking place within this substance are at the core of rheumatic complaints, lies at hand.

It is difficult to explain the lancinating, permanent discomfort observed in the inactive phases of the disease. The patient complains about cold, humid extremities, with a craving for warmth. Capillarmicroscopic examinations and those of the skin temperature afforded abnormal findings in regard to the circulation in the smallest blood vessels.

The latest arteriographic investigations of SEYSS and LEB point to spasms within the arterioles, though venous flow is unimpaired. Further experiments, including electrical registration of plethysmography and skin temperature

assays, indicate that perfectly healthy persons display a similar percentage of atypical vascular response. This fact denotes that circulatory alterations are in no way specific for rheumatic disease.

The fundamental question seems to be whether rheumatic pain — and so the pathological process — is caused by a primary disease of the collagen fibres and ground substance, or by some as yet unexactly determined disturbance of capillary circulation. In the first case the "P-factor", resulting from an undetected "rheumatic" change of the connective tissue is still a matter for future determination. In the second, we are justified in accepting anoxia as the responsible P-factor.

CO-RELATOR:

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Mucoid Substances in Degenerative Diseases of the Locomotor Organs

In degenerative diseases of the locomotor organs, examinations of blood and urine revealed the special behaviour of protein-bound hexoses as the most constant feature. Chemical examination of cartilaginous discs led to the same results. It is possible that the agent does not act only on the disc system, yet it is in the discs that the changes become permanent, on account of their peculiar mechanical conditions and deficient capacity for regeneration. Apart from a numerical decrease of the structural tissue elements, it should be assumed that osteochondrotic processes are associated also with a general rearrangement of the disc substance, as seen from the higher protein content and the increase of the demonstrated neutral polysaccharide.

The interrelations of the intervertebral disc systems and the organism should be studied on a broader basis. The present examinations have yielded certain data concerning the role of humoral factors and of infection.

The significance of physico-chemical examinations is emphasised especially in early alterations.

DISCUSSION

Collagen and Collagen Fibre

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The morphologists in their approach to the question of the nature of collagen precursors depart from the precollagen, which biochemists from the soluble collagen. Instead of closing, the gap is ever widening between these views. The morphologists have so far failed to reveal more about the fate of the precollagen than that it is "imbibed" with a "collagenous" substance. On the other hand, all the biochemists have focussed their attention on the various patterns of soluble collagen (NAGEOTTE 1931 ; TUSTANOVSKY 1947, 1949 ; HARKNESS et al. 1952 ; GROSS et al. 1951) setting aside the insoluble residue of collagen fibres.

The fibrous precipitates of the soluble collagen were compared with the whole native collagen fibre and have indeed shown striking roentgenostructural, electron-microscopical, and chemical similarities. Both of them have the same amino-acid composition (PLOTNIKOVA, TSHERNIKOV) ; they reveal the same diffraction maximum of 2.9 Å (HERZOG, FAURE—FREMIET, BEAR) and under the electron microscope display the same cross striation (640 Å). Histochemically, they posses identical properties (TUSTANOVSKY, ORLOVSKAYA 1955). In their native state both are trypsin-resistant (TUSTANOVSKY et al. 1952).

The first biochemical hypothesis relating to collagen fibre formation has been put forward by histologist (NAGEOTTE 1931). In his view the soluble collagen is deposited in the form of sedimentary fibrils under the influence of neutral salts.

This theory of collagen formation underlain by the clear idea of a sedimentation mechanism has recently somehow came to cede its place to a vague and nebulous concept of biochemists on a "transition" from the soluble collagen to the definitive collagen fibre (OREKHOVITSH, 1952). However, no views have as yet been advanced as to the mechanism of this "transition", nor has it been clarified what the "transition" product, *i. e.*, collagen, really is.

Responsible for the "transition" hypothesis are the labile nature of acid soluble collagen and the great variability of its forms in vitro the collagen extractable by acid buffers forms solutions, flowing and dense gels, pseudocrystals, membranes and fibres (TUSTANOVSKY 1949). On these grounds the hypothesis has been proposed that the collagen soluble in acid buffers is the "biochemical precursor" of tissue collagen; hence the designation "procollagen" (OREKHOVITS, TUSTANOVSKY, OREKHOVITS, PLOTNIKOVA, 1948 ; TUSTANOVSKY, 1949).

For the "transition" hypothesis formal support has been afforded by observations in vivo, according to which glycine labelled with C^{14} is incorporated into both soluble and insoluble collagen fractions at different rates. Three conclusions were postulated without sufficient criticism : 1. The procollagen and the collagen represent different proteins ; 2. the fibre residue left over after the removal of the procollagen represents the mature definitive collagen itself ; 3. the procollagen gradually "converts" into collagen via a considerable number of intermediate forms (OREKHOVITSH, 1952).

In the view of HARKNESS et al. (1952), the true biochemical precursor of collagen is not the procollagen, but the fraction extractable with phosphate at pH 9 (this is NAGEOTTE's collagen B). On the other hand, according to JACKSON (1957), and to GROSS et al. (1951), the true precursor is the fraction extractable by neutral salts. This fraction has been named "tropocollagen". In the assumption of these authors the tropocollagen produced by fibroblasts converts into procollagen from which the collagen then derives. The same authors reject the hypothesis of "transition" and suggest that the mechanism which underlies collagen formation is either an association of the soluble collagen protofibrils (adlineation) or a sedimentation of the precursors during their interaction with mucopolysaccharides and adenyl nucleotides. BANGA, BALÓ and SZABÓ (1956) have come to the conclusion that collagen formation can be traced back to the formation of an exceedingly intricate "protein-mucopolysaccharide complex".

Apparently, these hypotheses have also failed to approach the diverging views of the morphologists and the biochemists. The morphologists failed to understand why the concept

of „precollagen" should be entirely ignored. The simple fact that the appearance of definitive collagen fibres is really preceded by that of the precollagen fibres contradicts the direct formation of collagen from a soluble collagen. JACKSON (1955) had attempted to correct this defect, assuming that fibroblasts produce the procollagen which forms precollagen fibres : the terminal stage in collagen formation would be the imbibition of the precollagen with tropocollagen.

The precollagen problem has not been finally answered. In my opinion, ORLOVSKAYA and ZAIDES (1952) have been the first to approach the problem. They have established that before a certain age the precollagen fibres of the embryonic skin do not possess 2.9-Å diffraction ; in other words, that this important property of both the mature collagen and the soluble collagen fibres is absent in the precollagenous fibres. The precollagen acquires this eminently characteristic quality simultaneously with the loss of its argyrophilia and with the appearance of the morphological features of the mature collagen. These facts furnish in my judgement a real evidence that the principal proteins of the precollagen and collagen fibres differ in their structure, but the same facts have left open the question whether the alteration in the roentgenogram the due to the structural changes of the precollagen protein itself, or the appearance of the soluble collagen was responsible for this phenomenon.

In attempts to decide the latter point we subjected to complex histochemical analysis the residue of the native collagen fibre after removal of the soluble collagen. The findings concerning all three substances and their comparison are illustrated in Table I (TUSTANOVSKY, ORLOVSKAYA, and ZAIDES, 1954).

These data show that the properties of the fibre residue undoubtedly differ from both the entire collagen and the procollagen, but reveal no difference in their amino acid composition. We might conclude that both the proteins, of the procollagen and that of the insoluble residue differ from each other solely in the configuration of the polypeptide chains and are isomeric. This residue we have named "collastromin" indicating that it forms the "warp" of collagen. In studying the mode of combination of procollagen and collastromin we departed from the assumption that the interaction between them revealed the conjunction of the microphases : the procollagen layers represent the external microphase, and the collastromin filaments the internal one (TUSTANOVSKY et al., 1954). The adequacy of this assumption has been substantied by electron-microscopic observations (PÖTZ and NEMETSCHEK, 1956 ; WYKOFF, 1952, KENNEDY, 1955).

Table I

Properties	Collagen	Procollagen	Residue
Opt. microscopy			
a) Form	fibrous bundle	fibres and pseudocrystals	loosened bundles
b) Staining with : Foot's method	non-argyrophilic	non-argyrophilic	argyrophilic granules and bundles
toluidine blue	non-metachromatic	non-metachromatic	metachromatic
picrofuchsin	red	red	yellow
Electron-microscopy			
Smallest measurable unit in diam.	500—1000 Å	—×	50 Å (filament)
Cross striation	640 Å	640 Å	230 Å (infrequently)
Roentgenography			
Diffraction maximum of 2.9 Å	+	+	—
Of 640 Å	+	+	—
Amino acid composition very similar and	equally specific throughout		
Solubility			
a) in citrate buffer pH 4	20.25%	100%	insoluble
b) in solutions of neutral salts or alkalies	4%	—	insoluble
Thermal effect			
a) threshold temperature of contraction	67° C	dissolves without contraction at 50—55° C	55° C**
b) type of contraction	anisodiametric (decreasing in length, increasing in diam.)	dissolves without contraction at 50—55° C	isodiametric (decreasing in length and diam.)

* = smallest unit is the procollagen molecule = 14 Å in diam.
** = findings of I. BANGA.

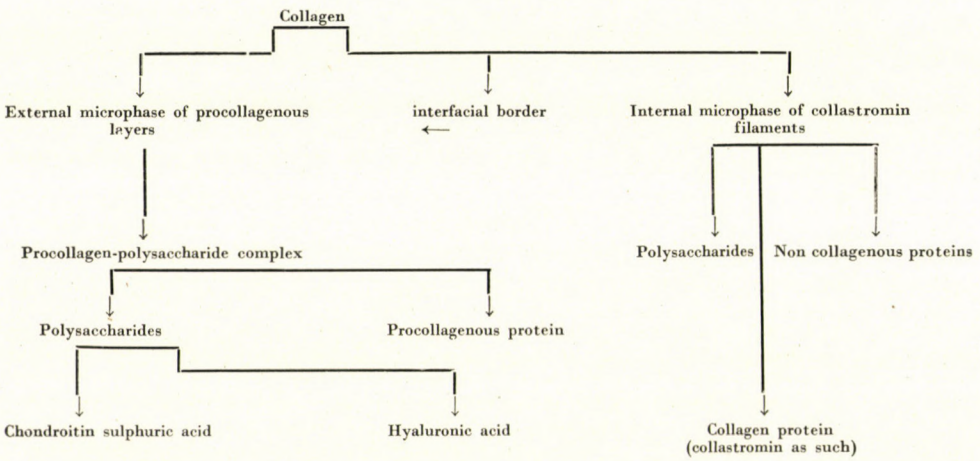
The structural and compositional data for collagen (primary collagenous fibril) are presented in Table II.

Every multiphasic substance is built up of some structural units. As regards collagen, this unit is the primary fibril, measuring in diameter from 500 to 1000 Å; it is simultaneously a biochemical and morphological unit (at the electron-microscopical level).

Table II

Schematic representation of the build-up of collagen

(Primary collagenous fibril)



The concept of the biphasic structure of collagen, and of the biochemical unit at the electron-microscopical level is unprecedented and has nothing to do with the multicomponent structure of collagen fibre. FAURÉ-FRÉMIET (1937) has been the first to surmise the bicomponent structure of collagen fibre. The multicomponent concept is professed also by BANGA (1954), and BANGA, BALÓ and SZABÓ (1956). Much attention has been devoted to our hypothesis, by these Hungarian investigators, but they regard as the ultimate unit of collagen not the primary collagenous fibril at the electron-microscopical level but the whole bundle of collagen fibres at the optical level. They consider the collagen fibre a homogeneous "chemical unit". Upon the action of heat or chemical substances this "chemical unit" disselves, with a portion of the mucopolysaccharides and the procollagen being set free in the process. Such a denatured residue was named "metacollagen" (BANGA, BALÓ, SZABÓ, 1956 a, a, c, 1957). The procollagen and the metacollagen should be combined at the molecular level by chemical bonds. In our view, metacollagen and collastromin differ from each other in principle : the first is the product of denaturation, the latter is the native structural element of the collagen unit. Collastromin and procollagen combine at the electron-microscopical level as two phases.

According to our data, each of the microphases of the collagen unit is multicomponental and includes mucopolysaccharides. In addition, in the structure of the collastromin filaments the argyrophilic proteins are wedged. The latter component is likely to cause the argyrophilia of collastromin filaments. We also have observed (ZAIDES et al. 1953) that the interaction between the mucopolysaccharides and procollagen is essentially a „tanning" process. If bound to procollagen at the normal ratio, the mucopolysaccharides give rise to a natural cross striation (640 Å) of procollagen fibres *in vitro* and of the collagen unit in tissue (outer layers of procollagen microphase). From the procollagen fibres which are poor or deprived of polysaccharides (inner layers of procollagen microphase) this striation period is missing.

The mode of interaction between the procollagen and the collastromin remains to be studied. The mucopolysaccharides presumably participate in this mechanism inasmuch as collastromin becomes metachromasic after procollagen has been removed, both *in vitro* and under pathological conditions, e. g. in the fibrinoid focuses. The collastromin phase yields 75 to 80 per cent, and the procollagen phase 20 to 25 per cent of the fresh weight of collagen,

while the portion of non-collagen proteins does not exceed 4 to 5 per cent, and the mucopolysaccharide portion amounts only to 0.5 to 1 per cent (BOWES, 1957).

We wish to emphasize that collagen and collagen fibre are two different things ; the collagen is synonimous with the primary collagenous fibril and constitutes a structural unit, an element of the collagen fibre.

Being the inner phase of collagen, it is conceivable that during fibrillogenesis collastromin arises before the procollagen layers. As it was expected precollagen and collastromin have several qualities in common : the typical X-ray diffraction 2.9 Å, and 640 Å striation are missing ; both substances are argyrophilic and metachromasic ; both fail to be dissolved by procollagen solvents.

Accordingly, all the data that characterize collastromin equally refer to procollagen (see "residue" in Table I).

All the available findings support the idea that collastromin arises in the form of precollagen. It remains to be decided whether collastromin is absolutely identical with precollagen or is a variant of the latter.

The data presented above tend to prove that during fibrillogenesis the precollagen is specifically enclosed by, or surrounded with, procollagen layers and stays or persists as the collastromin in the definitive collagen unit.

The metabolic processes in procollagen and collastromin differ from each other in type as well as in intensity (amino acid incorporation rate). The collastromin metabolises at a very low level. It cannot be excluded that the extremely low metabolic level of collastromin is an expediently reduced form of metabolism of the precollagen, which after it has been covered with procollagen layers performs the new functions in the mature collagen unit. The outer procollagen phase of collagen is in direct contact with the external environment and is therefore more exposed to wear. Procollagen consequently metabolises rather more intensely than collastromin.

The interrelation of precollagen and collastromin is a particular question of the whole problem in the relationship between the proteins (procollagen, collastromin, precollagen, reticulin, elastin, elastoidine, etc.) in onto- and phylogenesis. There can be no doubt about the transformation of precollagen into collastromin. The corresponding structural changes could not be essential. ROBB—SMITH (1957) has recently expounded our concept of collagen structure and drew some conclusions as to the relation between collastromin and reticulin. Such an interconversion is hardly believable considering the structural completeness of both collastromin and reticulin. The transformation of precollagen into reticulin is rather disputable ; the similarity of the roentgenograms (no 2.9 Å) of collastromin and reticulin (protein fibrils liberated from matrix) merit attention. On the other hand, the cross striation (640 Å) makes reticulin similar to procollagen but not to collastromin or precollagen (ZAIDES et al., 1955). The transformation of procollagen into reticulin requires at least the incorporation of fatty acids into the peptide chains of precollagen because these acids are the chemical constituents of reticulin chains.

Summaring up a few words should be said concerning the structural peculiarities of collagen, which determine the histochemical and electron-microscopical characteristics of the collagen fibres. They are determined by the procollagen because this forms the outer phase of the collagen fibril. This outer procollagen phase conceals the argyrophilia and metachromasia of the precollagen (resp. collastromin) fibres and causes them to convert into nonargyrophilic and nonmetachromatic collagen fibrils. Therefore, any disarrangement of the phases is manifested by changes in the histochemical and electron-microscopical characteristics of collagen. Thus the picrofuchsin reaction remains positive until a pathogenic process destroys the procollagen layer. The argyrophilic and metachromatic reactions will not turn positive unless the pathological process liberates the collastromin from the procollagen coating.

Our concept of collagen structure and collagenogenesis appears to be capable of eliminating the present uncompromizable rupture in the views of morphologists and biochemists. Evidently, further research should be based upon the fruitful co-operation between biochemists, biophysicists and morphologists, and upon their associated efforts to elaborate new histochemical methods on a large scale.

Fibrinoid Lesions in Connective Tissue

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Although fibrinoid has been described 80 years ago, the characteristics of its structure have not been clarified.

Most authors agree with NEIMANN in that fibrinoid is a result of the collagen fibres' destruction combined with the deposition of plasma proteins. Another group of authors are opposing this view, believing that only the amorphous ground substance participates in the origin of fibrinoid (ALTSCHULE, AUGEVINE, and others).

CLARK et al. (1936) who investigated the fibrinoid in the vessel walls and MOWAT (1947) who studied it in the rheumatic nodules, postulated that fibrinoid is fibrin. The fibrinoid in vessel walls can also arise as a result of the desintegration of smoth muscle fibres (ALBERTINI, 1954 ; MONTGOMERY, 1956 and others).

In our opinion, KLEMPERER (1950) was right in warning against the tendency to unificate the meaning of "fibrinoid", considering that fibrinoid differs in composition as well as in the mechanism of its formation from one disease to the other. For example, in disseminated lupus erythematodes the fibrinoid material may be a degraded nucleoproteid.

At the same time, many authors are evaluating lesions of the same character differently. This discordance has its explanation probably in the fact that the investigators generally regard collagen as a one-phase system. We have shown (TUSTANOVSKY, SEIDESS, ORLOVSKAYA, MIKHAILOW, 1954) it to be a multi-phase system consisting of many components. Our conception permits a more precise analysis of the composition of tissues displaying fibrinoid lesions.

The present paper deals with true fibrinoid only, *i. e.* with changes which take place directly in the structure of the connective tissue. Our data have been derived from histochemical analyses of connective tissue changes observed in acute rheumatic fever ; the object of the studies was the hearts in which we investigated the valves, endocardium, myocardium, epicardium, and pericardium.

The initial changes in the cardial connective tissue may be considered as "mucoid swelling" : the collagen bundles become swollen, loose, refringent and metachromasic. Metachromasia disappears in tissue sections treated with hyaluronidase.

Metachromasia is the integrated result depending upon the polysaccharides in the ground substance as well as on the polysaccharide components of the collagen complex in which disorganization of the surface phase has occurred. The latter is proned by staining with picrofuchsin which is faint, if the tissue has been previously treated with collagenase (see further below). Toluidin blue polymerization is due to the release of the polar group of the polysaccharides. Marked hydration of the mucopolysaccharides released from the collagen and the ground substance explains the appearance of swelling in the affected areas.

The condition in which only swelling is observed and metachromatic substances are seen to appear, may be still reversible. It is the stage of incipient collagen disorganization, and we call it the first stage.

As the process aggravates, connective tissue disorganization becomes more and more evident with the accumulation of substances normally not encountered in normal connective tissue. In the affected area the connective tissue is swollen and homogenous, displaying basophilic spots (hematoxylin and eosin). The nuclei of the fibrocytes are swollen, loosened, occasionally dim (kariolysis).

On treatment with picrofuchsin the tissue stains red, but reveals some yellow spots, the fibrillar structure is not visible. After treatment with collagenase, the red colour fades and much more yellow material appears. As has been shown previously (TUSTANOVSKY and ORLOVSKAYA) staining red staining with picrofuchsin is a specific quality of procollagen, and not of the whole collagen. On the other hand, collagenase digests the procollagen when it is eliminated from the collagen system which has been destroyed under pathological conditions. The disappearance of the red colour following treatment with collagenase points to large diffuse deposits of released procollagen in the affected areas ; at the same time collastromin staining appears yellow.

With toluidine blue, fibrinoid lesions stain metachromatically, but display some bluish grey areas. Following pretreatment with hyaluronidase, the metachromasia disappears in some places, but persists in other. Periodic acid Schiff staining is markedly intensive. In such areas focal deposits of fibrin are observed ; with azan the latter stains blue, with occasional red spots. The collagen fibres begin to possess argyrophilic properties. Similar connective tissue

lesions are demonstrable in every part of the heart : the valves, the annulus fibrosus, the endocardium and in areas adjacent to the myocardium.

These histochemical observations point to a disorganization of the collagen. It is the second stage in which the deposition of plasma-proteins (*e. g.* fibrin) adds itself to the grave lesions. Since it is only at this stage that fibrin can be revealed, the swelling of this type may only be considered as "fibrinoid swelling".

As regards the modern concept of the mechanism by which such connective tissue lesions arise, the following should be said. In rheumatism it is the connective tissue in which the specific exsudative processes take place. The hyperergic state gives rise to increased permeability in tissues and vessels on the basis of which and the influence of pathogenic bacteria the conditions are created which induce disorganization of the collagen and the mucoproteins of the ground substance. These changes take place essentially as a result of the effect of bacteria and tissue enzymes. The products of decomposition pass into the blood stream, where they become autoallergenic and enhance the development of exsudative and destructive processes.

Upon the action of the numerous factors, various substances accumulate in the affected area, some appear from the connective tissue, others from the blood. They include procollagen and other proteins and mucopolysaccharides separated from the collagen complex, proteins and mucopolysaccharides of the ground substance, blood proteins, active cellular substances, and the products of cell destruction. The accumulated substances convert in various ways. The procollagen and polysaccharide may form new abnormal combinations.

Fibrinogen is converted into fibrin and threads deposited between the connective tissue fibres. In another type of conversion the sulphurated acid mucopolysaccharides, liberated from the connective tissue compounds, interact with the plasma fibrinogen which may settle on the surface of the disorganized collagen fibres. These fibres are argyrophilic. A precondition of the collagen fibres to become argyrophilic is that the fibrin itself be argyrophilic (TUSTANOVSKY, ORLOVSKAYA).

Argyrophilia in reticulin fibres depends essentially upon cystine — containing proteins (plasma proteins — fibrinogen, albumin) deposited in their matrix (ORLOVSKAYA, TUSTANOVSKY and ZAIDES). This is apparently the mechanism of argyrophilia in the collagen fibres which, in the opinion of many authors, is the characteristic feature of fibrinoid.

Let us now consider the concept of the "fibrinoid lesion" of connective tissue according to the above view. On the evidence of our observations, in such lesions the collagen fibres participate directly. The following staining characteristics are common to fibrinoid lesions in the connective tissue : in sections stained with picrofuchsin yellow spots are visible, metachromasia is uneven, displaying occasional bluish grey areas ; fibrin is present and the collagen fibres are argyrophilic.

Inherent in the concept "fibrinoid lesion" is a chain of different conditions of connective tissue, all arising from the decomposition of the collagen and ground substance. The released protein and polysaccharide components of connective tissue combine with the protein and the substances of polysaccharide nature of the blood plasma, primarily with fibrinogen. So we cannot agree with the classification of fibrinoid as a "depolymerized mucopolysaccharide" (JUSTIN—BESANÇON), "ground substance precipitate" (ALTSCHULE and AUGEVINE), or "condensed fibrin" (MOWAT). Morphologically, the word "swelling" might be the best to characterize the fibrinoid change in connective tissue ; we therefore suggest the use of the term "fibrinoid swelling".

Tissue that reveals fibrinoid alteration, still remains viable tissue. This is confirmed by the fact that the organism fails to respond with a cellular reaction to such alterations.

Together with fibrinoid swelling, focal necroses occur in the connective tissue, a qualitatively different phenomenon, although in scientific literature both meanings are used to identify "fibrinoid".

This is the aspect of "fibrinoid necrosis" of the endocardium and the vessel walls. A mass of granules or globules, basophilic on staining with haematoxylin-eosin, is visible in the centre of such areas, with typically large basophilic cells situated at the periphery of these areas. Histochemical examinations point to the necrotic alteration of the collagen fibres. Fibrin is usually not encountered in the necrosed areas. On these grounds, it may be stated that „fibrinoid" necrosis really represents gravely progressive degeneration of the connective tissue.

Hyalinosis is probably the result of alterations in the previously disorganized connective tissue, during the stage of swelling. In such tissues there are no fresh deposits, of fibrin. Part of the proteins originating from the plasma is eliminated, while the rest remains in the focus of hyalinosis, changed in its composition.

Although in rheumatism the intercellular connective tissue changes are generalized, the gravest lesions are localized in the valves, the endocardium, and the tendinous cords.

In all these structures "chondroid tissue" is encountered, rich in chodroitin sulphate (TRETIAKOV, 1916 ; MEYER et al., 1956). In the development of pathological structures extreme significance is generally assigned to the chondroitin sulphates as compounds with a most intensive surface activity. The pathologically disorganized chondroid tissue forms, so to say the base for the deposition of the various proteins (dislocated procollagen, blood proteins) ; coarse conglomerates arise, differing in structure from normal fibrillary collagen.

Such formations usually represent sclerosis, — the terminal stage of the pathologic change. In the course of rheumatic fever progressive with remissions and repeated attacks, the various lesions described above are piled one upon the other until the grave pathological connective tissue disorganization takes place which eventually leads to sclerosis deformans.

On the Submicroscopic Structure of the Intercellular Substance in Connective Tissue

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By polarization microscopic methods (anisotropic staining and enzymatic procedures) it can be demonstrated that the elastic and collagen fibres consist of a system of protein and acid mucopolysaccharide fibrils. In the elastic fibres both components run a spiral course the thread angle being 45° in the aorta of the newborn and 20 to 25° in ox ligamentum nuchae. The amount of mucoid and that of the collagen components can also be estimated in various fibres. Their ratio, the so-called metachromatic index, ranges from 6.0 (mucoid collagen in disks) to 0.5 (skin). Young elementary fibres have a high metachromatic index which decreases with age and is a reliable indicator of differentiation, aging and other pathologic processes taking place in the intercellular substance of connective tissue. Reticulin fibres and basal membranes are further characterized by their orientated lipoid component, and thus represent not "precollageneous" but differentiated functional structures.

From the functional point of view, two different and opposite changes can be distinguished in the connective tissue. (i) At the sites of irritation and activation, the connective tissue fibres undergo mucoid transformation with increasing metachromatic index, with structural loosening and enhanced diffusion. (ii) The diminution of the mucoid component in the intercellular substance (decrease of metachromatic index) leads to sclerosis, whereby the conditions of diffusion are impaired and the depositing of proteins and lipoids ensues.

These opposite changes occurring in the connective tissue substance play a significant role in physiologic and morbid processes.

Histochemical Studies on a Microstructural Basis of the Aniline Reaction in Elastic and Collagen Fibres

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In histologic sections mounted in aniline the birefringence of elastic and collagen fibres undergoes certain changes : the elastic fibres show negative birefringence, while the collagen fibres appear positive or slightly negative, depending on their age.

If a diffusion inhibitor Canada balsam is added to the aniline, the aniline reaction of the collagen is blocked. After acylation the collagen fibres react to aniline like elastic fibres and invariably show strong negative birefringence. The increased reactivity of acylated collagen to aniline is probably due to a blockage of the OH- and not to that of the NH_2-side groups on the substrate since after reactivation of the OH groups by deacetylation with alkalic hydrolysis the aniline reaction disappears. It is presumably for this reason that the elastic fibres with their low hydroxyproline content react readily with aniline but poorly or not at all, with collagen which is characterized by high hydroxyprolin content. No change in the aniline

reaction of collagen was found after the following histochemical procedures : sulfatation, desamination, oxydation, splitting of the hydrogen and covalent bands. In sections, the prepared pro- and metacollagen fibres behave like collagen fibres in every respect.

The Action of Collagenase on Collagen Fibres in Vascular Walls

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In spite of its wellknown effect collagenase is rarely used in histological techniques, because of the many controversial data regarding its action and, partly, because the methods of demonstrating enzymatic activity (release of nitrogen, change of viscosity, quantitative changes, etc.) are biochemical rather than histological.

In the present studies, the toxins of Cl. perfringens 107—109 and purified collagenase were used. The action of the enzyme on the collagen fibres was examined by polarization microscopic methods: the organized character of collagen protein, and its decomposition by Ebner's phenol reaction and that of the organized mucoid components by anisotropic Rivanol staining. In native or alcohol-fixed embedded sections of aorta the decomposition of collagen due to collagenase could be well observed. Mucoid and its protein moieties were equally depolymerized. This observation also indicates that in the collagen, mucoid and protein constitute a combined system, because of which the enzymatic action presumably the protein component results in the decomposition also of the mucoid component. In agreement with data in the literature it has been found that the depolymerization induced by collagenase takes place more rapidly in the tissues of young subjects.

The Oedema-Inducing Effect of Disodium-Ethylenediamine-Tetraacetate (EDTA—Na_2)

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In the morphologic and functional stability of the capillary walls a prominent role is played by the calcium contained in the interendothelial cementing substance. Disodium ethylenediamine-tetraacetate, having an affinity to calcium, provides the possibility of studying the morphological and functional changes associated with the mobilization of calcium in the capillary walls. The subcutaneous injection of EDTA-Na_2 produces oedema. This is well demonstrated by the intravenous administration of Evans blue to stain the oedematous area. The degree of oedema can be determined quantitatively. The effect of EDTA-Na_2 cannot be neutralized either by antihistaminic substances or by the antagonists of 5-hydroxy-tryptamine. To explain its effect, it is assumed that EDTA-Na_2 binds the calcium of the enterendothelial cementing substance whereby the latter is loosened and permeability is increased.

Histochemical Examination of Intervertebral Disks

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In 19 individuals it has been examined whether the disks taken from different regions of the spinal column exhibit histochemical differences. No consistent and significant difference was revealed by the methods applied. In the disks of old individuals fat deposits occur. The fat which under normal conditions is finely distributed or bound, may be released in degenerative processes and become morphologically demonstrable. This points to fat being an essential component of the basic substance of disks.

Comparative Histochemical Examination of Fibrinoid Changes in Vessels

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Increasing attention has recently been focussed onto collagen diseases. Clinicians and pathologists have endeavoured to determine the properties of fibrinoid, a substance which in these conditions can be demonstrated by histomorphologic methods. The examinations, however, resulted in contrasting data as regards the origin, material character, and staining qualities of fibrinoid.

Our purpose was to study comparatively and in detail the vascular fibrinoid changes occurring in collagen diseases (panarteritis nodosa, disseminated lupus erythematodes, scleroderma, rheumatic fever), furtber in malignant nephrosclerosis, and diabetic glomerulosclerosis.

Applying numerous staining methods and histochemical procedures, it has been found that the fibrinoid present in the vessel walls in different diseases has identical histochemical qualities. Amount and distribution of fibrinoid in the vessel wall depend on age and the severity of vascular lesions. The fibrinoid originates, at least partly, from the lumen of damaged vessels. The assumption that fibrinoid is a degeneration product of the basic substance of connective tissue or smooth muscle fibres cannot be proved. Degenerative changes of the collagen connective tissue do not produce a substance which might be regarded as histochemically identical with fibrinoid in the vessel walls.

Rheumatic Bone-Changes in the Copper Age

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Paleo-pathologic examinations revealed articular disease to be one of the most ancient and widespread affections. The cases presented show that in the copper age articular bone-changes had manifested themselves with the same patterns that are encountered to-day. In the development of these morbid processes an important role should be attributed to factors originating in the organism, as these processes did not change in the course of many thousand years. On the other hand, diseases induced by bacteria and viruses are always changing, because the mutual adaptation of the pathogenic agent and the organism results in changes of the morbid patterns.

Rheumatic Changes of Bones and their Palaeodemographic Significance in the Copper Age

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The demographic, social and environmental relationships of some palaeopathological investigations carried out in collaboration with Dr. G. Gáspárdy have been discussed. In the early and late periods of the Copper Age, *i. e.* between 2500 and 2000 B. C., peoples that had migrated into Hungary from the South-East lived together with the aboriginal inhabitan t of the neolithic period. In recent years, experts of the Hungarian National Museum unearthes 230 skeletons in Polgár-Basatanya, Ágoston-puszta, Tápé-Lebő and Alsónémedi. As cond cluded from the skeletons' age at death, in Hungary the average life span in the Copper Ag-e was 30.5 years. From the skeletons the age distribution and the ratio of sexes can be computed ; the number of generations can be determined from the time of use of the cemeteries (250 to 300 years).

About 45 per cent of the Ad.-Mat. skeletons displayed bone changes, *i. e.* traces of rheumatic disease. The character and extension of the changes depended on the life conditions. As to the age distribution of rheumatic disease, its traces were already present in early adult age and its frequency increased until old age.

Clinical and Morphological Picture of Collagen Diseases

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We interpret the term "collagen disease" as covering all diseases characterized by progressive and systemic alterations of the connective tissue and vessels.

Since, in 1942, KLEMPERER, POLLAK and BEER had established the concept of collagen diseases, a great number of publications has appeared concerning this subject. Many conflicting theories have been advanced in the course of investigations, and the controversies were mostly due to discrepancy in the views concerning the clinical manifestation of collagen diseases, their morphology, the metabolic disturbances connected with the syndrome, as also the relationships between collagen diseases and allergic diseases.

As is known, the following diseases are regarded as belonging to the group under consideration : true rheumatism (rheumatic fever), rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, scleroderma and dermatomyositis.

That certain features are common to all these diseases was pointed out by KLINGE as early as 1932. ERICH, in a monograph published in 1952, came to the conclusion that while, aetiologically, collagen diseases are different from one another they reveal striking similarity as regards pathogenesis, clinical manifestation and the development of characteristic disturbances of metabolism. The literature contains numerous references to such similarity between collagen diseases (SYMMERS and other authors).

Examining vessels of various calibres in the cadavers of 12 persons who had succumbed to disseminated lupus erythematosus, HILL and MAGUEL encountered endothelial proliferation, necrosis of vessel walls and haemorrhages. Many of these cases showed also glomerulonephritis and endocarditis.

POLLAK, PIRANI, CLARK, PULOS, MOUERNE and STECKER reported on cases of lupus-nephritis and the results of their pertinent clinical observations, biopsies and necropsies.

Studying renal alterations in cases of scleroderma — progressive systemic sclerosis — FISCHER and RODNAN diagnosed in the renal vessels oedema of the walls, accumulation of mucopolysaccharides of the chondroitic acid type, and fibrinous changes.

Puncturing the bone marrow of 45 patients suffering from rheumatoid arthritis, SILLER, MONTO, ENSIGN, PEBUA and LOVETTE analyzed the substance drawn from it and encountered lupus cells in 11 cases. Of these, only in 2 were clinical symptoms of disseminated lupus erythematosus observable. The observations of these authors are most significant inasmuch as they confirm the assumption that certain features are common to the pathogenesis of all so-called collagen diseases.

D. FRIU, by the fluorescence method of COONS, succeeded in demonstrating a particular substance which corresponds to gamma globulin, reacts with desoxyribonucleoproteins and is situated in the cell nuclei of muscle fibres, vascular endothelium, serous membranes and the integument.

FILLET, LOSCALUTTO and ZIFF examined the serum of patients suffering from disseminated lupus erythematosus. They proved that the factor of this disease corresponds to a component of the gamma-globulin fraction and may give positive reaction also in patients suffering from rheumatoid arthritis.

SCHWARTZ suggested that haemagglutination with sheep-erythrocyte suspension is specific in cases of rheumatoid arthritis. According to him, a special rheumatoid agent, adsorbed to beta and gamma globulins, constitutes the haemagglutination factor in this reaction. SCHWARTZ, on the evidence of his investigations, regards this agent as antibody. LOSCALUTTO and ZIFF think that the "rheumatoid factor" may be isolated from the protein fractions of the serum.

TULLIN assumes that rheumatoid arthritis provokes the appearance in the organism of auto-allergens. The presence of which would explain both seroreaction and haemagglutination.

GOOD, ROTSTEIN, VOGAN and MAZITELLO observed three cases of typical rheumatoid arthritis, in all of which agammaglobulinaemia was demonstrable. These observations go to prove that the classic anaphylactic-immunological mechanism is not the principal characteristic of collagen diseases in general and rheumatoid arthritis in particular. It can be assumed that other disturbances in γ-globulin metabolism may also occur in collagen diseases.

TEILUM pointed to a connection between amyloid accumulation and rheumatoid arthritis. On the basis of bistological investigations and various experiments he came to the conclu-

sion that accumulation of amyloid may be ascribed to a dysfunction of the cells of the reticuloendothelial system. Deposition of amyloid is preceded by on increase in the amount of pyroninophilic substance in the cytoplasm of endothelial and reticular cells. Also substances of a protein-polysaccharide nature accumulate in the cytoplasm of the said cells.

It seems clear from these data that lesions of connective tissue and metabolic disturbances occurring in collagen diseases are strongly influenced by the humoral factor. It should be noted that, essentially, these disturbances are closely similar in all collagen diseases. The question whether such alterations are due to a common aetiological factor or whether different aetiological factors give rise to similar alterations remains to be decided.

COLLINS studied the aetiology of collagen diseases including rheumatism and arrived at the conclusion that a similarity of pathological reactions need not be due to common aetiological factors. COLLINS rejects the term "collagen diseases" and we are inclined to agree with his cautious attitude. He seems, however, to forget that, whatever the disease, all intracellular and extracellular occurrences have to be regarded as manifestations of one and the same fundamental process. In his theoretical considerations, COLLINS makes an attempt to substantiate the theory that to study rheumatism and, generally, collagen diseases is, essentially, a study of cellular pathology. The results of histochemical and histo-immunochemical investigations point to the probability that cells are directly involved in processes of internal metabolism. Such processes, however, take place not only in the cells themselves, as suggested by COLLINS, but in the intercellular substance as well. That this is so has conclusively been borne out by laboratory observations made by us in connection with collagen alterations as seen in rheumatism.

According to present knowledge, the collagen diseases have the following common characteristics. 1. Uninterrupted clinical course; systemic lesion of connective tissue and vessels. 2. Intercellular disorganization of connective tissue associated with variable cellular reaction. 3. Increased permeability of tissue and vessels. 4. Vascular lesions. 5. Metabolic disturbances. Most important among the latter are an increased concentration of gamma globulin and fibrinogen in the serum and an increased mucopolysaccharide level in serum and tissues.

The following general pathological processes in the vessel walls and the connective tissue are characteristic morphological features of collagen diseases.

a) Mucoid swelling,
b) Fibrinous alterations,
c) Fibrinous necrosis,
d) Hyalinosis,
e) Sclerosis.

Each of these symptoms occurs also in other diseases which explains why morphological descriptions and biopsies are insufficient to characterize collagen diseases. It follows that the term "collagen diseases" covers a clinical-morphological and not a purely morphological concept.

Having studied each separate disease included in the collective term of collagen diseases, we propose to point to their morphological unity in the following.

True rheumatism (rheumatic fever)

This is a disease which fully satisfies the "requirements" of collagen diseases from a clinico-morphological point of view. It takes a lengthy and uninterrupted course ; systemic lesion of connective tissue and vessel walls are demonstrable at every stage of the illness. In no case of true rheumatism are missing the following symptoms : mucoid swelling of varying seriousness, fibrinous alterations, hyalinosis and sclerosis. The lesions involve not only the heart and its valvular apparatus but are encountered in the articular capsules, renal vessels and the walls of the intestines as well. (STOIA.)

That the clinical course of rheumatism is continous is shown morphologically by the following observations : 1. Granulomata in all stages of development — from fresh nodes to sclerosis — can be found in the myocardium in every case. 2. Various dystrophic alterations of the connective tissue, of the collagen and its phases in particular, are observable. 3. Diffuse vascular lesions of different types can be seen. 4. The disease is accompanied by every form of connective tissue and vessel lesions, from the initial alteration which manifests itself with mucoid swelling, to the final sclerotic form, *i. e.* by what we collectively call the disorganization of connective tissue and vessel walls. Be it noted that cellular reaction of the macrophage type occurs with the greatest frequency in rheumatism.

Rheumatoid arthritis

is also one of the collagen diseases. It is principally characterized by the lesion of periarticular tissues and that of the vessels and the connective tissue of the heart and of other organs.

The course of the illness is continuous and chronic. Even in advanced cases fresh and newly-formed lesions (mucoid swelling, etc.) in the vessel walls and the connective tissue are constantly added to the old sclerotic alterations. Cellular reaction — in its nature an accumulation of macrophages and plasma cells — is very considerable in the area of damaged connective tissue and vessels.

Scleroderma

called also progressive systemic sclerosis, a typical collagen disease, shows all the attributes that have been mentioned in connection with true rheumatism and rheumatoid arthritis, with the only difference that in the disease under consideration it is in the connective tissue and vessels of the skin that the most conspicuous alterations are encountered. It has been shown with fair accuracy that the progressive and systemic lesion of the vessels and the connective tissue, as encountered in scleroderma, is demonstrable not only in the skin but throughout the organism. Let us add that processes of disorganization which develop in the connective tissue of patients suffering from scleroderma reveal certain peculiar features: dermal lesions show a focal arrangement, and a slightly metachromatic swelling of the collagen bundles is also observable. A simultaneously developing, focally arranged fibrinous swelling is followed by hyalinosis of the damaged areas. The said presence of foci admits of the inference that the permeability of connective tissues and vessels is not increased through the entire organism. Cellular reaction is far from being pronounced. In acute cases with a profusion of cellular infiltrates, the latter contain a great number of mast cells.

An abundance of the said morphological alterations as seen in the various organs and tissues offers a combined picture of old and new lesions.

Lupus erythematosus disseminatus

All characteristics of the collagen diseases described above in connection with true rheumatism and other diseases of the group at issue, such as a continuous course of the illness, the systemic lesion of connective tissue and vessels, a polymorphous picture of acute and chronic alterations in connective tissue and vessels, are encountered also in this disease. It is not solely in the skin that alterations are seen to develop. A polymorphous picture, similar to that observed in cases of scleroderma, is another characteristic feature of lupus erythematosus disseminatus. Vascular lesions show the symptoms of angiitis and capillaritis. Cellular infiltrates consist, in their greatest part, of plasma cells.

Periarteritis nodosa

satisfies, both clinically and morphologically, all postulates we have established for collagen diseases. A special feature is the predominance of vascular lesions. The cellular infiltrate is polymorphous. It should be noted that periarteritis nodosa is a syndrome which may occur either as an independent disease or — and this is more frequent — as the final phase of any of the other collagen diseases.

Aetiology

The aetiology of collagen diseases is still unknown. Streptococcal infection is presumably a significant causative factor. We wish to point out that there seems to be a close connection between the syndromes under consideration and a changed reactivity of the organism. That this assumption is correct appears to be substantiated by the fact that rheumatic fever and rheumatoid arthritis are associated with allergy. A prevalence of the allergic component in collagen diseases is indicated by the cellular reaction. Predominance of the allergic component and a consequent increase of cellular reactions are observable in the acute phase of rheumatism, periarteritis nodosa, lupus erythematosus disseminatus and rheumatoid arthritis. On the other hand, it is known that the allergic component is less pronounced in scleroderma, and that — consequently — the various manifestations of connective-tissue disorganization are followed by no, or only very slight, cellular reaction. Insignificant cellular reaction points to the probability that, in the various forms in which collagen diseases manifest themselves, the action of the allergic component may be diminshed or altogether absent.

On Some Potential Sources of Error in the Diagnosis of Tuberculous Spondylitis

Fr. Lenoch

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The anatomy of pulmonary phthisis had been described in the 17th century by FRANCISCUS SYLVIUS (FRANZ DE LE BOE, 1614—1672), a German physician, and the clinical description was published by RENÉ-THÉOPHILE HYACINTHE LAENNEC (1781—1826), the discoverer of auscultation, early in the 19th century. Although the anatomical and histological changes of tuberculosis had been clarified before the discovery of Mycobacterium tuberculosis, no advance could be made in the treatment of infections caused by that organism until 1882, when the pathogenic agent was isolated by ROBERT KOCH. After that time the presence of the Koch bacillus was of diagnostic value, whereas the diagnosis of the Koch negative cases remained rather uncertain.

In the first quarter of the 20th century radiological diagnosis began to replace diagnosis by percussion and auscultation and had reached such perfection that it was often overestimated. There was a tendency to claim that radiology was infallible in the diagnosis of pulmonary tuberculosis. It is often forgotten that radioscopy, radiography and even tomography ensure diagnosis in approximately 90 per cent of the cases, whereas in the remaining 10 per cent the conclusions drawn by the radiologist may be erroneous. The harm this may do is illustrated for example by the reports of PAULTRIER on patients treated for years in tuberculosis sanatoria, although they had been actually suffering from Besnier-Boeck-Schaumann's disease.

When I point out the dangers arising from the overestimation and misinterpretation of the evidence obtained by radiological diagnostic procedures, I do it emphasizing that radiological diagnosis is the second best means for diagnosing tuberculosis ; the detection of Mycobacterium tuberculosis being the decisive evidence.

The diagnosis of tuberculosis of the bones and joints is much more difficult, because even when radiography is supplemented by tomography the evidence obtained is far less reliable than in the case of the respiratory organs. In pulmonary cases the chances of error in radiological diagnosis average 10 per cent, as compared to 50 per cent in cases of bone disease. It is true that the chances of error are reduced in advanced cases, but it is just in the early phase of disease that diagnosis should be accurate, at a time when the lesions to the bone, and joints are not yet severe and adequate treatment may bring about full recovery.

Those valid for the tuberculous affections of the skeletal system in general, apply even more markedly to tuberculous spondylitis. The spine is one of those parts of the skeletal system least suitable for detailed radiographic study. Ventrodorsally, large masses of soft tissue are projected on it and laterally it is at a great distance from the film. As a result, the quality of the radiograph is far from what would be desirable. This explains why radiography as a diagnostic aid lags far behind the clinical manifestations of spinal tuberculosis. It should be realized that a cherry-sized cavity in the body of a lumbar vertebra may be absolutely invisible in the radiograph. Also, osteoporosis of the spinal column can be recognized only after some 60 per cent of the calcium content has been lost. Thus, the sensitivity of the method is poor and can be relied upon in advanced cases only. From this follows that a negative radiographic finding is of little, if any, diagnostic value in ruling out some affection of the spine. Just as in any other field of medicine, also here the establishment of a negative diagnosis is much more delicate and responsible than that of a positive one.

It is almost impossible to diagnose Pott's disease in its early phase by radiological techniques and the clinical symptoms and signs invariably create the impression that the lesion had for long been in existence before radiology showed any deviation from normal.

The first radiological change is a narrowing of the intervertebral space, which, however, occurs in various forms of infectious spondylitis (typhoid, staphylo- and pneumococcal) as well, and is therefore not pathognomonic for Pott's disease. Yet, if we find this change in the anteroposterior or particularly in the lateral radiograph, tuberculous spondylitis should be suspected. The commonest site of origin being the body of a vertebra, the narrowing of the space between two adjacent vertebrae will occur only when the central caries of the vertebral body has attacked the upper or lower surface of the vertebra. This third, we may say early, sign, the destruction of the surfaces of the vertebra, appears as an irregular line in the lateral and sagittal views alike.

We do not wish to discuss here the more advanced lesions, such as angulation of the spine due to a collapse of affected dorsal vertebrae, destruction of one or more intervertebral discs, collapse of lumbar vertebrae, cold abscess formation, because these occur in a stage in

which diagnostic errors are less common. These advanced lesions cannot be mistaken for those involved in the pathological conditions we wish to deal with here.

What we intend to emphasize is that in its early phase tuberculous spondylitis may be suspected to be present, but cannot be diagnosed with certainty. It is true that it is more advantageous for the patients if we think of tuberculous spondylitis more often and if we accept this diagnosis even when not absolutely confirmed, emphasizing that this tentative diagnosis must be corroborated or replaced by another as soon as possible.

Long experience has shown that rheumatic affections are often confused with tuberculous conditions of bones and joints. This is particularly valid in the differential diagnosis of Pott's disease, in which ankylosing spondylitis is extremely difficult to rule out. The latter condition does not occur in children or in very old age, but may present almost insurmountable differential diagnostic difficulties in tuberculous spondylitis of the young adult.

Both diseases may cause sciatic pain or girdle pain, which may cease completely, only to reappear after various lengths of time. Loss of weight and signs of pulmonary tuberculosis may occur in the early phase of both conditions. Local pain caused by pressure and especially by tapping is less common in rheumatoid spondylitis, though it may be present.

Rigidity of the spine is likewise a common symptom. Long before the appearance of the minutest radiological change the spine is obviously restricted in motion due to muscle spasm. However, careful examination will detect a difference between the two conditions. The patient with tuberculous spondylitis will bend forward cautiously, whereas the sufferer from ankylosing spondylitis presents a contracture of the dorsal muscles and immobility of the spine but he carries out all movements without hesitation.

In ankylosing spondylitis the thinning of the intervertebral disc is such an uncommon occurrence that its presence may rule out the diagnosis of this condition.

As to osteoporosis, that due to Pott's disease is restricted to the body of the affected vertebrae, whereas in ankylosing spondylitis it tends to be generalized, involving the spine as a whole or even the pelvis. The transparency of the spine with normal intervertebral spaces is often described as the "glassy osteoporosis" of ankylosing spondylitis.

It is clear from what has been said above that in the early phase of these diseases differential diagnosis may be extremely difficult and even the most experienced clinician may commit errors. For this reason the diagnosis should be revised time and again.

In Pott's disease immobilization in recumbency is essential. This treatment is not noxious in certain conditions which may be mistaken for Pott's disease, but it may cause considerable damage to the patient with ankylosing spondylitis. Thirty years of experience in this field has tought me that exercises carried out conscientiously day after day throughout life are essential in the treatment of ankylosing spondylitis and if the joints showing an unusual tendency to ankylosis are immobilized, the patients, usually young men, soon become invalids.

If a patient with ankylosing spondylitis is diagnosed to suffer from Pott's disease and the not uncommon pain felt in the hip joints is considered to be a secondary coxalgia, immobilization in plaster will almost certainly lead to ankylosis in both hip joints and lower extremities.

From our clinical material we have selected 10 patients (8 males and 2 females) from among the most severely affected ones. These patients had been under treatment for 3 to 19 years for what was believed to be Pott's disease but was in fact ankylosing spondylitis. The more important data in regard to these cases are shown in *Table I.*, from which it is clear that it took an average of 10.2 years to correct the erroneous diagnosis.

Although mobility could to some extent be restored in these severe, advanced cases, even years of suffering and treatment could not restore the original condition.

One of these case histories is presented in brief.

R. J., born in 1924. Case history No. 410/57. Personal and family history noncontributory. In October, 1951, effusion of the left knee developed overnight, with pain on walking. The complaints having not changed, the knee joint was punctured and the left leg was immobilized for 6 weeks. After removal of the bandage the knee was more swollen than before. The skin covering that area was red and intense pain was felt when trying to move the knee. Sodium salicylate and ointments failed to produce any effect. Specific disease was suspected and the patient was transferred to the Department of Surgery in Bratislava, where he was treated with streptomycin, blood transfusions and repeated articular punctures. In October, 1952, also the right hip joint became painful. This was considered to be coxalgia and the patient was transferred to the Vyšne Hágyi tuberculosis sanatorium in the High Tatra, where treatment over a period of two years included immobilisation in plaster of Paris, streptomycin, penicillin, paraarminosalicylic acid, isonicotinic acid. The process gradually spread to both hip joints, knees, temporomaxillary joint and the joints of the feet, resulting in a complete loss of motility in all but the temporomaxillary joints. In 1954 Professor Sitaj examined the patient and diagnosed the Scandinavian form of ankylosing spondylitis. Two treatments in Jáchymov (a spa

Table I

Initials	Born in	Onset of disease	Plaster bed, months	Condition	Final diagnosis established in	Iritis
1. R. J.	1924	1951	24	Complete ankylosis	1954	0
2. K. A.	1916	1938	18	Ankylosis of spine, restricted motion in both hips	1946	+
3. J. V.	1901	1934	several	Ankylosis of spine, both hips and knees	1952	0
4. B. C.	1925	1945	24	Ankylosis of spine and left hip	1958	0
5. M. M.	1916	1939	10	Immobile, ankylosis of spine and right hip joint	1956	+
6. P. S.	1926	1942	6	Ankylosis of spine, both hip and knee joints	1946	+
7. M. A.	1908	1937	15	Ankylosis of spine and right hip joint	1950	0
8. L. M.	1918	1947	15	Almost complete ankylosis of spine	1951	0
9. K. A.	1913	1932	5	Ankylosis of spine and hip joints	1949	0
10. D. M.	1931	1948	5	Ankylosis of lumbar spine and hip joints	1953	0

with radioactive water) were ineffective. In 1956, the patient was transferred to our Institute. At that time he was an absolutely immobile cripple, unable to help himself in the smallest measure.

Clinical examination of the internal organs revealed no deviation from normal. The patient was absolutely immobile, recumbent, "stretched out" in bed. There was complete ankylosis of the spine, hip joints, knees and ankles, with the feet in the equinus position. The toes were fixed in excessive plantar flexion and were ankylosed in every joint. The motion of the right humeroscapular joint was substantially restricted, that of the left one was normal. There was ankylosis of the elbow and wrist joints. The erythrocyte sedimentation rate was 76 mm in 1 hour and 120 mm in 2 hours. The Bordet-Wassermann and gonococcus complement fixation tests were negative.

Treatment. More than 20 operations had to be performed on the legs of the patient before any attempt at walking could be made. Two years of strenuous work put the patient back on his feet and walking with crutches could be begun.

The fate of the other nine patients was just as miserable. The disease begins in young age and we must do everything in our power to avoid diagnostic errors that may cause such tragedies. Here, like in every field of medicine, prevention is better than the cure.

The conclusions drawn may be summarized as follows. 1. In tuberculous spondylitis the clinical signs and symptoms occur far in advance of the radiological changes. 2. The so-called early radiological changes, never allow to establish a final diagnosis, but are useful pointers in making a tentative diagnosis. 3. Clinicians and radiologists tend to ignore this rule and once they have made up their minds to treat the patient for what they believe to be a tuberculous spondylitis they fail to revise the diagnosis time and again, although this ought to be done. 4. No diagnostic error may be so detrimental for the patient as the confusion of Pott's disease with ankylosing spondylitis. If a patient in the early phase of ankylosing spondylitis is erroneously treated for what is considered to be Pott's disease by immobilization in plaster of Paris, this will have extremely grave consequences. 5. In every case suggested of being one of Pott's disease, a radiograph should be made of the sacroiliacal joint, this being the articulation in which the radiological changes of ankylosing spondylitis are detectable at the earliest time. 6. Although both diseases lead to spinal rigidity, especially obvious on forward bending, there still is a difference in this respect between the two conditions. When bending forward, the patient with Pott's disease bends the knees and tries to support his spine by placing his hands on the thighs. When returning to the erect posture, he "climbs up his thighs". In contrast with this, the patient with ankylosing spondylitis leans forward without hesitation and support. In the early phase, the patient with Pott's disease may find a hard bed and recumbency comfortable, whereas the one with ankylosing spondylitis may be forced to get up at night to obtain relief by exercise. 8. The possibility of ankylosing spondylitis should be considered in every case when an adult, especially a young one, is suspected of suffering from Pott's disease. 9. In ankylosing spondylitis (Strümpell, Pierre Marie, Bechterew's disease) every joint has an increased tendency to ankylosis if immobilized for long periods of time. 10. Fixation in plaster

of Paris will create an immobile invalid from the patient with ankylosing spondylitis. Rehabilitative efforts may bring some improvement in years, but even then the patient will be far from being a normal individual capable of managing himself. 11. It must not be forgotten that even the diagnosis of pulmonary tuberculosis, as determined on the basis of clinical and radiological evidence, is but a tentative one, although the probability of correct diagnosis is estimated at 90 per cent. This fundamental principle applies in an even greater measure to bone tuberculosis in general and to tuberculous spondylitis in particular. Here the diagnosis is considered to be tentative in the early phase, the probability of error being nearly 50 per cent.

The only evidence establishing the diagnosis is, and will remain in the future, the detection of Mycobacterium tuberculosis.

An Anatomical and Clinical Survey of Atypical Forms of Gout

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Classic forms of gout are rarely encountered in the Roumanian People's Republic. Arthroses with gouty diathesis, *i. e.* with increased uric acid and cholesterol concentration in the serum, used to occur fairly frequently in the past, especially in the case of corpulent female patients in the menopause. Of recent, we have had occasion to observe a number of male patients aged from 40 to 60 years who showed various forms of primary chronic polyarthritis with a negative Rose—Heller test and elevated uric acid level. These symptoms disappeared after the usual gout therapy. We have, therefore, subjected atypical forms of gout to a special study, the results of which are presented in the following.

Gout represents a disturbance in nucleoprotein and purine metabolism. WALLACE GRAHAM suggested that gout was transmitted to America from Europe: in Canada the number of persons afflicted with gout is rising, while that of patients suffering from acute and primary chronic polyarthritis is diminishing. BROCHNER—MORTENSEN reported on the frequent occurrence of gout in Denmark and South Sweden.

We have frequently encountered, especially in aged male patients, not only arthroses with hyperuricaemia but also infectious rheumatism with hyperuricaemia, and we feel certain that many an atypical form of gout is still undiscovered. It is a rule in our clinic for rheumatics to determine the uric acid and cholesterol level in the serum of all patients — in particular of those over 40 years of age — who are admitted with painful, degenerative and inflammatory afflictions of the locomotor apparatus. It has helped us in correctly diagnosing many atypical forms of gout showing the symptoms of articular or extraarticular inflammatory of degenerative rheumatism. Gout usually occurs between the ages of 20 and 60 years but we know of a case, accompanied by the formation of tophi, which occurred in an infant of 5 weeks and another which was diagnosed in an old man 90 years of age. Gout is hereditary.

Although it is known that uric acid is deposited in the tissues, the question whether the symptoms of gout can be attributed to such deposits is still undecided. While deposits of urate are responsible for tophi and articular deformations they do not release gouty attacks. Factors that can be regarded as the actual provocators of attacks are operations, injury, alcohol, faulty diet, physical or mental overexertion, intercurrent infectious diseases and various medicaments such as liver extracts, mercurial diuretics, insulin, ergotamine, gold preparations, vitamin B_1, vitamin B_{12}, ACTH, etc.

Gout may be associated with obesity, arthrosis, diabetes, hypertension and urolithiasis.

Certain conclusions we had reached in the course of our investigations were pointed out in a lecture held at the Congress at Marianske Lazne (Marienbad) in September last, under the title "Treatment in Roumanian spas of rheumatic diseases and affections of the locomotor apparatus associated with urolithiasis". They were as follows. 1. Certain rheumatic affections may be accompanied by diverse forms of urolithiasis; 2. such affections associated with urolithiasis are, in a descending order of frequency, arthrosis with gouty diathesis, periarthritis, fibrositis, primary chronic polyarthritis and Bechterew's disease.

The following atypical forms of gout have been described by BESANCON, M. P. WEIL and DE GENNES : 1. the pseudophlegmonous form, associated with widespread oedema, which may show the symptoms of suppurative arthritis or those of a genuine abscess ; 2. hydrarthrosis, mostly in the knee, with profuse discharge, chronic course and long duration ; 3. a poly-

articular form similar to infectious rheumatism ; 4. the pseudotuberculotic form resembling tumor albus ; 5. progressive gout with successive attacks involving all joints.

PUIG-LEAL, VALLADO and GUON BUNOS refuse to accept the view that gout is gradually disappearing ; what actually happens is that it mostly appears in atypical forms, *e. g.* as acute or primary chronic polyarthritis, as secondary rheumatism or as monoarthritis. Atypical forms of gout develop, according to DE CHÂTEL, without attacks and are accompanied by asymmetric articular deformations.

While having frequently had occasion to observe cases of acute gouty hydrarthrosis in the knee-joint (one of these cases took the form of suppurative pseudophlegmonous arthritis with extended swelling), we have not encountered atypical forms imitating acute articular rheumatism. Often have we observed acute lumbar pain in corpulent persons which was accompanied by fever, hyperuricaemia and hypercholesteraemia, symptoms which disappeared after adequate gout therapy. We have, futhermore, frequently encountered atypical forms of gout which had the appearance of a tumor albus of the knee-joint and were associated with hydrarthrosis, hyperuricaemia and hypercholesteraemia : all these symptoms likewise disappeared on the usual gout therapy. It often occurs that pycnic patients suffering from hyperuricaemia and hypercholesteraemia with eczemas (especially over the elbow) are tormented by pains all over the body, mostly during the night : gout assumes in these cases the form of fibrositis and responds readily to specific treatment.

Gouty inflammation of the Achilles tendon is well-known : it manifests itself with pain in the heel and disturbances of locomotion, is of a short — at the most of a week's — duration and responds well to treatment with colchicine.

We have had further numerous cases of gouty aponeurisitis plantaris with skin eruptions, as also cases of bursitis olecrani with gouty eczemas.

According to a statistical table compiled by KUZELL and GAUDIN, primary chronic polyarthritis appears together with gout in 5.4 per cent of male and 7.7 per cent of female patients.

Uricaemia is a frequent diagnosis in cases of primary chronic polyarthritis.

Bechterew's disease has been found to be accompanied by gout in 4.8 per cent of male and 3 per cent of female patients.

We have frequently diagnosed hyperuricaemia and hypercholesteraemia in patients over 50 years of age who were suffering from primary chronic polyarthritis.

Patients suffering from articular gout sometimes develop ophthalmic complications such as conjunctivitis, iridocyclitis, episcleritis and sometimes dermal complications in the form of eczema, chronic pruritus or — in some cases — in that of thickened toe nails with calcium deposit.

In chronic gout, tophi are formed 3 to 10 years after the first attack.

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Our knowledge concerning the pathological anatomy of gout is still far from complete. It is generally accepted that deposits of monosodium urate provoke alterations in the tissues.

TALBOTT and POMMER regard synovitis as a primary and chondral damages as a secondary lesion in cases of gout. Crystals of monosodium urate if the synovial membrane and those central areas of the articular cartilage which lack a sufficient blood supply, further deposits of the said substance in the form of large agglomerations if the subchondral bones are encountered. The cartilage shows traces of erosion and seems to be thin ; the synovial membrane may change into a fibrous pannus which penetrates into the articular cartilage and the subchondral bones and destroys the osteotrabeculae. Such destruction is markedly stamped in roentgenograms. In serious cases, pannus may lead to bony ankylosis. The sharply outlined figures in the roentgenograms represent, as a matter of fact, gouty tophi in the bones. The activity of the osteoblasts is stopped by the deposits ; while readsorption of the bone is unchecked, the formation of fresh osseous tissue comes to a standstill and no regeneration of bone takes place in the vicinity of the tophi. By means of a long treatment with Benemide it was, nevertheless, possible to reduce the size of tophi and provoke a recalcification of the bones destroyed by them. Osteophytes are sometimes observed to develop on the margin of the affected articular surface ; urate deposits may lead to a thickening of subchondral bones or to colloidal oedema and a necrosis of the tissues.

In cases of acute gout we encounter crystallized or amorphous masses of urate on the synovial membrane and in the articular cartilage, with inflammatory reaction in their surroundings : this develops later into granulation tissue. It consists of phagocytes, monocytes, giant cells, leukocytes, eosinophilic cells, polynuclear cells, lymphocytes and plasmocytes. On the periphery of this "gouty granuloma" are fibroblasts and a fibrous capsule which envelops the

tophus and the large urate deposits. These deposits give no X-ray shadow, are unlike bone, remain white and markedly outlined. There are small sclerotic vessels in their neighbourho od, which become sometimes obliterated by endothelial proliferation. The vessels are surrounded by small infiltrates composed of lymphocytes and plasmocytes.

Besides crystals of monosodium urate, sometimes cholesterol is encountered in the centre of the tophi ; deposition of urate is sometimes followed by that of calcium. The synovial fluid contains leukocytes, especially polymorphocytes ; increased viscosity and protein content of the fluid are additional symptoms.

Tophi may form in any organ : they have been encountered in the eye, the corpus cavernosum, the praeputium penis, the tongue and epiglottis, the vocal cords, the mitral valves, in the aorta and the myocardium. Areas with diminished blood supply are places of preference for the formation of tophi, and painful inflammatory reactions invariably develop in their vicinity.

Nodes of monosodium urate — or, in children, of ammonium urate — are sometimes formed in the kidneys : they are really uric acid infarcts. Sometimes also vascular sclerosis will develop, followed by atrophic lesions and fibrosis of the glomeruli and changes of the tubular epithelium. Nephrosclerosis is more frequent in gouty than other patients. It seems that deposition of urate in the medulla and the pyramids, further an obstruction and compression of the collecting tubules with subsequent nephrosclerosis are the chief factors responsible for renal lesions in gouty patients. Cases of renal amyloidosis have also been reported.

Inflammatory processes of cellular reaction in the surroundings of urate deposits develop only in areas with a rich blood supply, *e. g.* in the synovial membrane or the bone marrow where osteogranulomata are formed, whereas no cellular reactions occur in regions poor in blood, *e.g.* the articular cartilage. While no deposits of urate have been encountered in the muscles, lungs, the liver, spleen and the central nervous tissue, they were observed in the vicinity of the spinal canal.

Cystic structures in the bones or proliferative alterations as marginal prominences, development of spurs and local osteoporosis in the vicinity of the affected joints being not specific symptoms of gout, diagnosis of this disease should not be based solely on X-ray evidence. Prompt and satisfactory therapeutic results are sometimes the clue to correct diagnosis. Nor is, as a matter of fact, hyperuricaemia an infallible sign of gout. Laboratory analyses are often revelatory: the ESR is increased in acute cases of gout, leukocytosis and anaemia can be diagnosed, and the excretion of 17-ketosteroids with urine is lessened in younger patients suffering from gout.

Acute articular rheumatism, primary chronic polyarthritis, arthrosis, tumor albus of the knee-joint, gonorrhoeic arthritis, secondary infectious arthritis, calcium gout and cholesterol gout are diseases that may be mistaken for gout.

We want to emphasize once more that although in our days the classical type of gout seems to occur less frequently than in the past, its atypical forms have become more frequent so that in cases where the usual gout therapy fails it is always advisable to turn our attention to possible atypical forms of the disease.

Allergic Granulomatosis

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After a short review of the pertaining literature the clinical pattern and the gross and microscopic changes observed in a case are reported. The disease group is discussed mainly from a morphologic aspect (characteristic granuloma, vascular and renal alterations), but due regard is given also to the possible aetiologic factors and to the allergic-hyperergic mechanism. Finally, the possibility of diagnosis in the living is treated on the basis of literary data and of the case observed (from lymph nodes, cutaneous and subcutaneous nodules, excised lung lobe, prostatic biopsy).

Contributions to the Pathohistology of Dermatomyositis

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The muscles of two female patients who had died of dermatomyositis were studied. The disease had lasted, with remissions, for 16 and 18 months, respectively. Both patients had died in the course of an acute exacerbation. Sedimentation rate had been around 100 ml/1 hr, and gammaglobulins had been considerably increased in both cases.

In the skeletal muscles of Patient 1 (18 muscles were examined) infiltration consisting of lymphocytes, partly of histiocytes, a few leucocytes and eosinophils, were found both around th e vessels and diffusely in the perimysium and in parts of the endomysium. The muscle fibres exhibited nodular and floccular degeneration, fragmentation of fibrils, invasion of the sarcolemma cells, probably histiocytes. The number of muscle fibres was greatly reduced, the amount of connective tissue moderately increased. No mucoid or fibrinoid degeneration was observed.

In the muscles of Patient 2 (14 muscles were examined), inflammatory infiltrations were rare, only a few lymphocytes were seen in the adventitia of the perimysial capillaries. The muscle fibres were, however, reduced in number. They displayed various degenerative changes, and were invaded by a mass of histiocytes. So-called collagen changes were not observed.

These observations suggested that the affection and loss of muscle fibres is not a consequence of the so-called collagen disease of connective tissue, but the same factor which leads to the alteration of connective tissue produces also the lesion of muscle fibres.

Pathomorphology of Pulmonary Changes in Collagen Diseases

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The pulmonary changes were studied in 26 cases of collagen disease (polyarteritis nodosa, 10 cases ; disseminated lupus erythematodes, 5 ; scleroderma, 4 ; necrotizing polyangiitis and granulomatosis, 5; rheumatoid arthritis, 3; rheumatic fever, 1 case). The pathomorphology of the changes occurring in the pulmonary parenchyma, vessels, and bronchi, have been demonstrated simultaneously.

None of the changes was found to be characteristic of any one collagen disease. All morphologic signs were, though to a varying degree, observed with all collagen diseases. The morphologic changes in the lungs should therefore be classified according to structural types. Such types are : the pneumonitic, the granulomatous-necrotic, and the sclerosing types.

The pneumonitic type most frequently occurred with rheumatic fever and DLE. Granulomatous-necrotic alterations were found chiefly in polyarteritis nodosa, necrotizing polyangiitis and granulomatosis. The sclerosing type was mostly a concomitant of scleroderma and rheumatoid arthritis. All these types appeared not only in one certain morbid pattern, but occasionally in all, in dependence on the rate of progression of the process.

Pneumonitis may occur not only in acute, but in every kind of collagen disease, during the acute period. In spite of the acute histologic signs, pneumonitis is not invariably malignant. More malignant is the granulomatous-necrotizing type. It is apparently, the morphologic manifestation of a subacute exacerbating process, and in benign conditions it may be a sign of progression. Finally, apart from chronic collagen diseases, the sclerosing type may attend also rheumatic fever and occur in patients who survive recurrences of DLE.

The various pulmonary changes associated with the collagen diseases obviously represent similar morphologic phenomena. In the individual pathologic processes they display quantitative rather than qualitative differences.

Examination of Early Renal Changes by Needle Biopsy with Particular Regard to the So-Called Collagen Diseases

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Of the early renal changes examined by percutaneous needle biopsy, special attention has been paid to those associated with disseminated lupus erythematodes. Partly so-called "wire loop" lesions were revealed, partly changes corresponding to focal glomerulonephritis. In contrast to general opinion, the latter changes were the more frequent, the more characteristic, and these had given rise to a more extensive destruction of renal tissue. Much resemblance was found between the observed changes and those occurring in renal amyloidosis or diabetic glomerulosclerosis. The difference was that in DLE the deposits elicit an inflammatory reaction in the wall of the glomerular loops.

Morphologic Signs of Paraproteinosis in Disseminated Lupus Erythematosus

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It is known from the examinations of KLEMPERER et al. (1941—1954) that the main feature of disseminated lupus erythematosus is the precipitation of atypical protein-like substances in tissues. According to EHRICH (1952), dysproteinemia is a common sign of collagen diseases and it plays a prominent part in their genesis, whereby this disease group is closely related to primary amyloidosis. The resemblance of the hyalinosis occurring with DLE in the spleen and kidneys, and para-amyloidosis, has been pointed out by Teilum (1948—1956).

In the present study, in the kidneys, spleen, and lymph nodes, transformation of extracellular fibrinoid into paraamyloid-like fibrillary structures has been observed, together with such an excessive intracellular protein accumulation in spleen and lymph nodes which has been known to occur only in multiple myeloma (plasmocytoma), and macroglobulinemia (Waldenstroem), thus in the most characteristic instances of paraproteinosis. On the basis of these observations, fibrinoid degeneration (fibrinoid necrosis), known as a partial phenomenon of necrotizing inflammation in DLE, is regarded as the primary precipitation of atypical proteins, and conclusions have been drawn as to the pathogenesis of DLE.

Takayashu's Disease, Verified by Biopsy

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Progressive obstruction of the large arteries originating from the aortic arch leads to a gradual cessation of pulsation in the upper extremities, symptoms of cerebral ischaemia, ocular changes (cataract, atrophy of iris, blindness). The syndrome develops mainly in aged persons, as a sequel of syphilitic aortitis or arteriosclerosis (with or without an aneurysm). In young age, nearly exclusively females are affected. The disease characterized by the obstruction of supraaortic vessel stems is called "pulseless disease", "aortic-arch syndrome", "pulsus differens". The obstruction of large arteries in young women is termed "young female arteritis".

Slowly developing obliteration of the left subclavian artery has been observed in a 21 year-old female patient. The pulsation of the subclavian, axillary, brachial, and radial arteries had ceased. The diagnosis was confirmed by arteriography. The obstructed part of the artery was resected and thoracic sympathectomy was also performed. Histology revealed aspecific giant cell panarteriitis. As to the aetiology, tubercolotoxic allergy was assumed.

The case reported as well as those like it form a separate type of the aortic arch syndrome and the name Takayashu's disease is suggested to denote them. The reported case was the first by which the diagnosis of Takayashu's disease was confirmed through biopsy.

Pathologic Observations at Cardiac Surgery

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In sixty cases which had been subjected to cardiac surgery with a fatal outcome, clinical and pathological data were studied with special regard to the cause of death. The material consisted of thirty-two cases of mitral stenosis, sixteen of Fallot's tetralogy, 5 of auricular septal defect, 3 of coarction of the aorta, 2 of aortic stenosis, and 1 of persisting Botall's duct. Death was due to cerebral, pulmonary, peripheral, or air embolism in thirteen cases. In fourteen cases ventricular fibrillation or standstill of the heart during operation led to death. Heart failure occurred in sixteen cases. In seven cases death resulted from hemorrhage, nine patients died of other causes, and in one case the cause of death could not be stated for certain. The frequency of lethal factors is discussed on hand of literary data and own observations, together with the methods by which these occurrences can be eliminated or their frequency reduced.

Morphologic Signs of Allergy in Erosions of the Portio Vaginalis

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In the authors' opinion, allergic factors may have an essential role in the genesis of diseases of unknown aetiology. This is corroborated, apart from clinical observations, immunbiologic and serologic examinations, also by pathomorphologic studies. In previous examinations, beside the well-known morphologic manifestations of tissue allergy (serous inflammation, fibrinoid transformation), a proteinlike substance resembling Russel's corpuscles was found to appear extracellularly in cases of peptic ulcer, chronic nephritis, etc. From these morphologic signs was to the presence of an allergic condition concluded.

Five hundred cases of erosion of the portio vaginalis were examined. In 76 (15 per cent of the total), characteristic granulation tissue occurred below the cylindric epithelium of pseudoerosions, between cervical glands, and below the lining epithelium of the cervical canal. This granulation tissue was made up of lymphocytes, neutrophil and eosinophil leucocytes, and numerous plasmocytes. The cytoplasm of some mononuclear elements contained an accumulation of small eosinophilic globes and similar globes of protein were situated extracellularly. Considerable vascular alterations were revealed. The walls of the small capillaries displayed protein imbibition and at many places fibrinoid necrosis. There was an extensive oedema, and the collagen fibres were also imbibed with protein. On the basis of the earlier observations and literary data, these changes are regarded as the morphologic manifestations of an allergic resp. auto-allergic tissue reaction. Allergic diseases were mentioned in the history by 60 per cent of the patients with erosion. Beside this general allergic factor, the role of a local antigenic effect must also be presumed. Such an effect may be exerted by the foreign proteins of bacteria, fungi and, occasionally, by those of the sperm.

Pertaining serologic and immunobiologic investigations are in progress.

Significance of Foci and Focal Infections in the Pathology of Rheumatic Diseases

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The clinical symptoms of early and late allergy, generally tuberculin type allergy, frequently appear in the various rheumatic diseases. In the early period, *vegetative* (neurodystrophic, neurovasal, tropohoneurotic, etc.) disturbances prevail. Later, *humoral* (blood count, serum proteins, immunologic) and *histologic* (inflammation, degeneration, regeneration) changes are prominent. The role of foci in these processes has been shown by an increasing number of data. The decomposition products of foci (endoallergens, aggressins) seem to deserve more attention than bacterial and toxic allergens. In the course of the present studies, 2007 patients suffering from chronic rheumatism were studied. They had been admitted for hydrotherapy. Apart from clinical examinations for foci, desensitization experiments with focal extracts were carried out. Increased attention was paid to the hitherto neglected urogenital foci.

In a material consisting of 1765 male patients, suspicious dental foci were found in 19.6 per cent, laryngological changes in 36.1 per cent, prostatitis in 33.5 per cent. In this "suspicious" group, making up 73.2 per cent of the total, many patients yielded a positive response to 2, a few to 3 examinations. The prostatic secretion of 366 patients was examined bacteriologically. Haemolytic staphylococci, beside other agents, were found in 76.8 per cent, haemolytic streptococci in 38.7 per cent.

From the organs suspected to contain a focus and from their secretions, extracts free of protein and amino-acids containing 5 mg nitrogen per 100 ml were prepared. These extracts were used for intracutaneous desensitization. To control the results, the vegetative symptoms, local, general, and focal reactions, sedimentation rate, antistreptolysin titer and titer of C-reactive protein, were taken into consideration. A parallelism was observed between the clinical course and the laboratory findings. After treatment for 3 to 4 weeks the patients of the parasympathergic vegetative type became free of complaints, or considerably improved. Stress is laid on the fact that this therapy is simple and harmless, and no drugs or procedures exerting undesirable side-effects are needed. In order to settle the controversions regarding the role of foci, the continuation of these examinations is suggested. Pathologists, clinicians, and immunologists should define the criteria of focus. The results of desensitization and of the removal of foci should be controlled with laboratory findings, not only in rheumatism, but also in other allergic diseases. Finally, the relationships of the individual foci should be studied.

Mitosis Promoting and Inhibiting Substances in Bionecrotic Livers of Rats

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The rat liver is a proper organ for studying regenerative processes. The course of such processes has often been described from a morphological and biological aspect, but their aetiology has been mostly neglected. PODWYSSOTZKI and his pupil MEISTER in Kiev had carried out functional stimulation of the liver ; their method, however, was described rather inaccurately. Nevertheless, they observed that mitoses occurred most abundantly at the junction of healthy liver tissue and the resected stump.

Later it was observed that the liver of an animal living in parabiosis can be stimulated by the partial excision of the liver of the partner. This means that a substance is present in the circulation of the partner that acts on the intact liver. Where is this substance produced? The comparison of MEISTER's results with the recent findings suggestst hat it is produced in the necrosed stump.

To prove this, we ligated the two large lobes of rats' liver, but did not remove them. The abdomen was closed. After 48 hours (when the number of mitoses reached its peak) we removed the liver and examined the regenerated tissue for mitoses. 10 animals were used in these experiments. 5 animals with their left and large hepatic lobes removed served as controls.

The results have been tabulated. The number of mitoses was calculated per 0.06/cu. mm liver substance. The number of mitoses was on the average 162.9 in the experimental animals, 48.8 in the controls. The difference is statistically significant ; the mitosis stimulating substance

is obviously produced in the necrosed stump. The greater the stump, the higher the number of mitoses.

Next, the necrosed liver part was examined by biochemical methods, for the closer investigation of the substance in question. Proteins were separated from fats and split to albumin and globulin. Fats were examined after separating the glycerides, stearides, phosphatides and cerebrosides. All components were tested. Proteins proved ineffective, and so did the products of their splitting. On the other hand, the intraperitoneal administration of fats was followed by are increase in the number of mitoses and lesion of the liver parenchyma. The administration of glycerides and stearides revealed the substance eliciting mitosis to be harboured by this mixtures. Phosphatides and cerebrosides had no or only a slight effect, while they produced typical lesions manifesting themselves with marked erythro- and leucodiapedesis around the central veins. The biochemical examinations are still in progress, but a few results may already be reported. The substance stimulating mitoses becomes in the course of chronic administration gradually ineffective, presumably by eliciting tachyphylaxis.

Mitosis in the rat liver can be stimulated also by certain unsaturated organic compounds, *e.g.* penicillic acid.

The Effect of Allergic Reaction on Mitotic Activity

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Among the many phenomena of mitosis, little is known of the factors which promote or inhibit the multiplication of cells under physiological conditions. The results of the numerous investigations into the action of various chemical and physical factors on mitotic activity, on the physiological and pathological neogenesis of tissues, have suggested that most of the factors examined had no influence or inhibitory effect on cell growth. All that is known with a reasonable degree of certainty is that mitotic activity is increased by some agents of protein nature, such as nucleic acid, homogenisates of cell nuclei and mitochondria. We have found vitamin B_{12} to possess such an effect.

According to ERICH et al., antigens entering the body are taken up by the resting reticulum cells, which undergo repeated division, then turn into antibody-producing plasma cells. Accordingly, mitosis were an important link in the chain of the reactions against antigens. Starting from this consideration we have examined the effect of certain proteins and of the allergic reaction on the mitotic activity of such tissues which to our knowledge do not take part in antibody formation.

Mice, rats and guinea pigs from our own inbred stock were used. The animals were killed by lighting gas. Mitosis was studied on the intestinal epithelium and corneal epithelium, in sections 7 microns thick, embedded in paraffine. In the duodenum we recorded the number of mitotic nuclear divisions per one cross section and in the corneal epithelium the number of mitoses in the basal row of nuclei.

Serum from healthy horses and bovines was used as the antigen. Glucose-broth cultures of Streptococcus pyogenes haemolyticus were treated by prolonged shaking and freezing, using the material thus obtained (that contained bacterium body, toxins and exoenzymes resistant to the treatment mentioned) in the experiments.

In the intestines of mice, 0.2 ml of horse serum injected intraperitoneally caused a slight increase in mitotic activity in the early phase. There was no significant difference after 6 to 12 hours, but in 24 and 48 hours mitotic activity was significantly increased. The intestinal and corneal epithelium of mice and guinea pigs previously sensitized with horse serum showed no changes after 6, 24 and 48 hours.

In mice and guinea pigs sensitized with the bacterial material mentioned above, intraperitoneal doses of 0.4 and 2 ml caused no change in the mitotic activity, as determined 6 and 24 hours after injection. The same applies to those animals which had not been pretreated.

Most authors ascribe the allergic reaction to a liberation of histamine. In further experiments we therefore investigated the effect of histamine on intestinal mitotic activity. We injected into guinea pigs 20 to 40 mg/Kg, and into mice 1000 mg/Kg of histamine intraperitoneally, repeating these doses 2 to 4 times. In the animals sacrificed 5 hours after the first injection

of histamine mitotic activity was increased. The subsequent doses caused no change in the guinea pigs, whereas in the mice mitotic activity was decreased.

It has been concluded that in the course of the allergic reaction there occurs no liberation of substances which would significantly influence mitotic activity. In support of this view is the observation that in the viscera examined a single dose of histamine increased the number of mitoses whereas repeated doses did not.

The Morphogenetical Role of Polyblasts in Rheumatic Lesions

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The involvement of histiocytes in the rheumatic myocardial nodular and non-nodular lesions and epicardial lesions has been investigated.

Myocardium. The nodular myocardial lesions of the Talalayev, Klinge or Aschoff type are characterized by a clear delimitation of the affected area, even when the nodule shows a tendency to scar formation and central fibrosis. The diagnosis is based on the presence of single big, hyperchromic, mostly mononuclear, sometimes polynuclear histiopolyblastic elements. The lymphopolyblasts are much smaller, round, and have hardly any stainable body. Both the blood vessels and the interstitium enclosing them are apparently normal, except for a certain kind of lymphoblastic infiltration.

Nodules of the Aschoff type may be found. Big histiopolyblasts, appear, made epitheloid in shape by the compression of the cell masses.

In the non-nodular lesions there are no sharp outlines, transition from normal to pathological is gradual, the cells composing the lesion are of the same type, though local differences may occur.

Preaortic epicardium. A histologic section of the intrapericardiac aorta was examined. This area was covered by a fine white film, the serosa was dull and hyperaemic, and the base was relatively dense. Microscopic examination showed that only a small part of the endothelium was normal. Under the serosa, proliferation, groups of hyperchromic cells of polyblastic histioid nature were visible, at sites showing epitheloid forms. The blood vessels are dilated, ample haemorrhage and diffuse oedema are visible. This is an example of hyperplastic rheumatic serositis.

The ventricular epicardium may become the site of intense fibrovascular connective tissue organization, as shown by the presence of a sero-fibrinous exudate. Cells of Anitchkov (peculiar cells, which should be described in more detail) are detectable.

Microscopically under high power fibrinoid material surrounded by macrophages and lymphoblasts are visible and oval nucleus. The nuclei are kidney or finger-biscuit shaped, with deep indentations. The cell membrane is distinct, the chromatin either adheres to it, or is aggregated around and between the 2 or 3 nucleoli.

Neither these light oval nuclei nor the corresponding cells are in connection with the fat-containing cells.

By turning the micrometer the chromatin can be followed radially or in minute clumps from the centre to the cell membrane, within which it may form a well-defined stratum, making the nucleus similar to a heap of vacuoles separated by fine chromatin films. The nuclei of these Anitchkov cells are readily differentiated from the lymphopolyblasts, which vary in size depending on the quantity of cytoplasm.

In the same case (that of an adult) the *fibrous pericardium* shows an extensive detachment of the endothelial lining in an area corresponding to that of the epicardiac deposits. Even the remaining parts are detaching, hyperplasia, round nodules are visible. There are newly formed capillaries with swollen nuclei, heaps of lymphocytes and fibrocytes between the fibres of connective tissue. The subjacent capillaries are dilated and surrounded by abundant lympho and histiopolyblastic infiltrations. Resting fat cell vesicles are also seen. The fibres are driven apart by superficial oedema. In deeper strata the oedematous areas are comparatively chromophilic. Gross examination revealed a dull surface and about 100 ml of serofibrinous fluid.

The histiopolyblasts play a well-known role in the genesis of nodular rheumatic lesions. We wish to emphasize the importance of non-nodular infiltration, described by Romberg (1894), Norman Moore (1899), Poynton and Payne (1900), as a non-specific lesion.

In contrast with this, our investigations begun in 1932 indicate that the non-nodular infiltrations containing lymphopolyblasts of varying size, as well as hyperchromophilic histiopolyblasts with extensive homogeneous body are qualitatively identical with the Talalayev, Klinge and Aschoff type nodules.

Studies of these histiocytic elements has made it possible to elucidate the rheumatic nature of certain non-nodular infiltrations. Such infiltrations were demonstrated at the Filantropia clinic in striated muscle, in cases of verified rheumatism (Danielopolu), as well as in various visceral lesions, in rheumatic polyserositis.

More recently, the team of N. Hortolomei obtained by auricular biopsy as yet unpublished evidence that, in accordance with the clinical observations, these non-nodular lesions were of a certain diagnostic importance in rheumatic diseases. Thus, auricular biopsy makes it possible to establish the diagnosis of rheumatic fever even in the absence of characteristic rheumatic nodules of the Aschoff type.

We consider the Aschoff nodules with hyperchromophilic (hyperbasophilic) histiopolyblasts and the giant cells to be the lesions characteristic of rheumatism. The morphogenetical explantation may be an adaptation aimed at the mobilization and absorption of fibrinoid in the metabolism of histiocytes. In fact, fibrinoid necrosis is a gelification process and absorption is not accompanied by the usual phenomena of protracted absorption, such as phagocytosis, granulocytic invasion, appearance of fatty substances.

The classical studies initiated by O. WARBURG showed that both normal and pathologic growth takes place by the utilization of carbohydrates (sugars).

In rheumatic diseases the depolymerized mucopolysaccharides formed in the course of the genesis of fibrinoid material constitute a part of the fundamental pathochemical process.

Under the conditions of tissue allergy such as prevail in rheumatic disease, in which not only completely soluble organic compounds (*e.g.* glucose) but also pseudosolutions (*e.g.* complex amino acids and corresponding macromolecules) play a role, the depolymerization of mucopolysaccharides results in colloidal gel formation. This is the so-called fibrinoid. At the first glance its optical qualities make it similar to fibrin, but its staining and biological behaviour (for instance total absorption, etc.), but particularly its dependence on desmogen, desmofibres and desmocytes indicate quite a different pathochemical nature. (Antigen specificity, the anatomoclinical variants of genesis.)

The Aschoff type giant cell is considered in rheumatic disease to be a mastocyte, a cell in which the accumulated material is not granular, but is homogeneously mixed with the cell body. This is what according to A. I. STRUKHOV (personal communication, 1956) gives the positive staining in Hotchkiss—Mc Manus' reaction.

These Aschoff type cells grow to reach a giant size without mitosis or amitotic division, as a result of an apparent blocking of the mitotic ability of the cell or at least of the nucleus. But, and this has not been realized, these giant cells disappear without any of the known signs of lysis, picnosis or rhexis. The Aschoff nodes themselves disappear completely and are replaced by scar tissue, the Aschoff cells decrease gradually in size and are digested, liberating the materials contained in them.

The cells of Anitchkov were observed to occur under various conditions. They are present in rheumatic lesions, in myocarditis due to typhus fever. However, in rheumatic myocarditis they are present exclusively under the endocardium (in the granulation tissue formed from organized fibrin), whereas in myocarditis associated with typhus fever they can be detected anywhere in the myocardium, at the periphery of Meynet's (Fränkel's) nodes and in the infiltrates alike.

In rheumatic fever the presence of fibrinoid draws the histiopolyblasts of the myocardium into a special metabolic and morphogenetical cycle. At the level of the epicardium, in the absence of fibrinoid nodules, the perivascular histiocytes may assume the form of Anitchkov cells, under conditions as yet unknown. — In contrast with this, in typhus fever no change of this kind is visible in the myocardium, thus the perivascular histiocytes may take up the form of Anitchkov cells anywhere.

Contributions to the Pathology of the Connective Basic Substance

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(State Institute of Rheumatology and Medical Hydrology, Budapest)

In an atypical morbid condition belonging to the group of rheumatoid arthritis and associated with diffuse mesenchymal reaction, disproteinaemia, contracture in the knee joint, and the sclerosis of connectíve tissue in the environment of the joint, further inactivity, gave rise to crural oedema and later, to circumscribed elephantiasis of the foot. A tissue sample from the foot was examined histologically. Scattered round structures reminiscent of concrements, 50 microns in size, were found. They were Schiff-positive, showed metachromasia with cresyl violet, stained also with Weigert's fibrin stain, and gave an intense positive reaction to Kossa's silver stain.

As the metachromasia did not disappear on treatment with hyaluronidase, the fibrinoid must have contained a metachromasic substance, probably a highly depolymerized mucopolysaccharide, in which secondary lime precipitation had taken place.

The question was raised whether the fibrinoid had formed there or it had been transported from another place into the subcutis of the foot. Considering the calcification, the change was not recent. So, had it been formed there, it would have been surrounded by a cellular reaction. However, fibrinoid was found in the sections independently of inflammatory foci and scattered among intact fibres. It is therefore assumed that the substance had been transported to the subcutis of the foot, where the disturbed circulation allowed it to become fixed.

Chemical Changes in Connective Tissue in Artificial Inflammation

Ö. Schulhof, A. Richter

(State Institute of Rheumatology and Medical Hydrology, Budapest)

The changes in the chemical composition of skin were studied in the area of Shwartzman's phenomenon. A slight increase in the content of proteins and a significant increase in those of hexoses, hexosamins and uronic acids was found. The amount of neutral and acid polysaccharides was also increased.

The solubility of this substances is hindered in the area of inflammation, where neither intravenously injected Evans blue, nor bromsulphalein was observed to escape.

Physicochemical changes occuring in the inflamed area seem more important than the quantitative ones. Special attention should be devoted to the changes in solubility conditions, which are more conspicuous than those occurring in chemical composition.

Action of Histamine on the Polysaccharides of Serum and on the Alcohol-Soluble Mucoproteins in Diseases of the Locomotor Organs

A. Richter, B. Bányai, L. Éliás

(State Institute of Rheumatology and Medical Hydrology, Budapest)

Histamine exerts a pronounced effect on the polysaccharide system of serum. This effect is more marked in patients suffering from some inflammatory disease of the locomotor organs. Chemical and electrophoretic examinations have shown that primarily the carbohydrate content is influenced by this effect, whereas the ratio of the protein fractions undergoes no change. The change in the carbohydrate content takes place mostly at the expense of the alcohol-soluble mucoproteins. Chromatographic examination of the mucoproteins has been discussed together with the eventual role of the histamine effect in the genesis of diseases of locomotor organs.

Significance of the Rheumatoid Factor

L. Kovács, S. Bozsóky

(State Institute of Rheumatology and Medical Hydrology, Budapest)

By the use of positive and negative standards prepared from sera of patients suffering from primary chronic polyarthritis, and sera of healthy control individuals, the optimum conditions for the demonstration of the rheumatoid factor had been established and a micromethod for the demonstration of the factor has been worked out. The procedure allowed to demonstrate the presence of the factor in the serum of 90 per cent of patients suffering from primary chronic polyarthritis. In secondary cases the reaction was always negative. The demonstrability of the rheumatoid factor is greatly promoted by the absorption of heterophil agglutinins by means of sheep erythrocytes.

The diagnostic value of the Rose reaction is reduced by the fact that the rheumatoid factor cannot be demonstrated before the late stage of the disease, when already primary chronic polyarthritis can mostly be recognized from clinical symptoms, but it certainly offers some help in diagnosing atypical patterns. Among 50 patients suffering from atypical chronic polyarthritis the rheumatoid factor was determined in the sera of 18. It is believed that the disease of these 18 patients was atypical primary chronic polyarthritis, rather than some particular morbid process.

Peculiar Changes of Fibres in the Lymph Nodes of Patients Suffering from Lymphogranulomatosis Treated With Chemotherapeutic Drugs

L. Holczinger, K. Lapis, J. Sugár

(Research Institute of Oncopathology, Budapest)

The lymph nodes of patients suffering from lymphogranulomatosis and treated with Degranol for prolonged periods were examined by histologic, histochemical, and polarization optic methods. It was found that the cell population characteristic of lymphogranulomatosis had been entirely or partially destroyed by chemotherapy. In the lymph nodes there appeared a fibrous substance arranged in bundles, connected with the reticular fibres. These bundles gave the same histochemical reactions as the reticular fibres. In polarized light the bundles were revealed to be made up one part of an isotropic substance containing widely scattered small elementary fibres showing a positive birefringency like collagen fibres. The observed change seems to represent an intermediary phase of the transformation of reticular fibres to collagen fibres.

Changes in the Intervertebral Disks in Acute Rheumatism

F. Korill

(City Hospital, Balassagyarmat)

Intervertebral disks play a prominent part in diseases of the spinal column, *e. g.* in spondylosis deformans. This disease is generally believed to be due to degenerative changes in the disks.

Necropsy of a 9 years old child revealed rheumatic pancarditis, with early Aschoff's nodules in the myocardium, and cellular infiltration in the annulus fibrosus of disks. The infiltrations were made up of eosinophil cells, histiocytes, multinucleated giant cells, and lymphocytes. In another case, a boy aged 11 years, the remnants of rheumatic endocarditis, and Aschoff's nodules in the myocardium, were found. Beside these, a connective tissue septum protruding into a disk gave rise to the detachment of a segment of the annulus fibrosus. The septum protruding into the disk was infiltrated by lymphocytes.

Thus, in cases of acute rheumatism there occur in the disks infiltrates like Aschoff—Talalayev's nodules. Restitution takes place by cicatrization. The rupture of the scar may form the base of spondylosis deformans. In contrast with the general opinion reflected in the literature, some cases spondylosis deformans may be of rheumatic origin.

SECTIONAL MEETING

I. Morphological Subjects

Anatomic Moulds Made of Polyvinyl Chloride

A. Gellért, I. Z. Konsánszky

(Dept. of Anatomy and Embryology, Medical University, Szeged)

Polyvinyl chloride was used for making anatomic moulds. PVC powder "GM" lends itself well to this purpose ; it contains also a stabilizator ensuring the durability of the model. For softening, dibutyl phthalate is used. It is thoroughly mixed with PVC, then a dye is added to reproduce the colour of skin. The ready model is coloured by painting its surface.

The models are made as follows.

(i) A plaster of Paris cast is made from the prepared region.

(ii) From the cast a paraffin-wax positive is made and this is reshaped so as to correspond to the original preparation.

(iii) From the paraffin-wax model a plaster of Paris negative is made.

(iv) The ready PVC mass is cast into this negative and hardened at 150° C.

The main advantage of PVC moulds over those made of paraffin-wax is their elasticity. Not being fragile, they can be used in teaching without the danger of destroying the model.

12 moulds have been presented at the session.

Experiments to Influence the Cytomorphologic Reactions of the Adenohypophysis Deprived of its Hypothalamic Connexions

K. Kovács, M. A. Dávid, I. W. Horváth

(1st Dept. of Internal Medicine, Medical University, Szeged)

The question was examined whether or not the direct hypothalamic connexions have a decisive role in the cytomorphologic reactions of the adenohypophysis. To this end, the adenohypophysis of rats was tranplanted into the anterior chamber of one eye (autotransplantation), and the histologic structure of the graft was studied after such procedures that induce characteristic histologic changes in the normal anterior lobe.

In the transplanted organ gradual dedifferentiation took place. The basophil cells disappeared, the eosinophils decreased in number, a chromophobic pituitary gland was developed. Following formalin administration, which in the normal adenohypophysis induces an intense basophilic hyperplasia no change occured in the cytomorphologic pattern of the transplanted dedifferentiated organ. On the other hand, cortisone administration resulted in the appearance of basophil cells in the graft. This basophilic hyperplasia could be prevented by follicle hormone. If thyroidectomy have been performed at the time of transplantation, no thyroidectomy-cells appeared. Thyroidectomy-cells already present in the adenohypophysis disappeared after transplantation. Similarly castration cells did not develop in the transplanted adenohypophysis, and the castration cells already present in the normal adenohypophysis as a sequel of preceding castration underwent regression : after the interruption of hypothalamic connexions, the pituitary being in the state of gonadotrophic hyperfunction undergoes gradual dedifferentiation. This process can be accelerated by folliculin.

These results admit the conclusion that hypothalamic connexions play a prominent role in the control of the cytomorphologic reactions of adenohypophysis. This hypothalamic control is, however, not at all exclusive ; there being factors exerting a direct influence on the organ, independently of the diencephalon.

Influence of Hypothalamic Injury on the Healing of Fractures

I. Földes, Cs. Kósa, Á. Orosz

(Dept. of Anatomy, Histology and Embryology, Medical University, Debrecen)

The course of regenerative ossification and the possibilities of influencing it have been studied. The role of minerals in the healing of fractures has not been clarified ; regarding the effect of calcium, contrasting data have been reported. The role of the nervous system has not been established either.

In previous studies it had been found that lesion to the tuberal part of the hypothalamus results in hypercalcaemia, the peak of which is attained after two weeks. A slight increase in the serum phosphorus level was also observed. The calcium and phosphorus content of bone did not change significantly.

In the present experiments the effect of hypercalcaemia on the healing of fractures has been studied. In 29 rats weighing about 150 g each, the left femur was broken, then the fragments were fixed with an intramedullary nail. The course of healing was examined after 1, 2, and 3 weeks. The pars tuberalis of the hypothalamus was injured in all cases two weeks before the examination of fracture healing. In the control animals, the examination of fracture healing was undertaken 4 weeks after the hypothalamic lesion, *i. e.* at a time when hypercalcaemia had already ceased. The examined tissues from both the experimental animals and the controls were stained with haematoxylin-eosin or azan and subjected to histochemical procedures (Hotchkiss, Ritter—Oleson).

The site of cerebral injury was controlled by serial sections.

Results

(i) Two-week-old injury of the hypothalamus exerted a favourable action of healing : the cartilaginous callus appeared earlier, and was greater, and new bone formed quicker, than in the controls.

(ii) The effect of hypothalamic lesion was favourable also in the 2nd week, in contrast to the data in the literature stating that calcium enhances fracture healing only in the first week. This points to an influence of the nervous system.

(iii) The histological findings were corroborated by the results of histochemical reactions. The transition from Hale-positivity to Hotchkiss positivity was particularly rapid in fractures of the animals injured two weeks previously.

(iv) Callus formation in the animals injured 4 weeks previously was much slower than in those with two-week-old lesion, or in the controls. This slowing down was most manifest in the third week after fracture. For this, the following may have been responsible. a) The high calcium level may inhibit metachromasia, *i. e.* the appearance of Hale's acid mucopolysaccharides. At the time when Hale-positive substances are missing, fracture healing may be inhibited. In the animals injured 4 weeks before, the bone was namely broken at the time when hypercalcaemia was at its peak. b) The role of the nervous system must also be considered. 4 weeks after the injury, counterregulatory functions may appear, to compensate the failing activity of the injured area.

v) To decide the above problem, further experiments are in progress. For instance, healing of fractures will be studied 6 weeks after performing different lesions.

Mechanism of Cartilage Formation by Neodifferentiation

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Cartilage formation by so-called neodifferentiation occurring in the adult was studied by the half-joint method of Krompecher-Puky. In dogs, the cartilage together with a few mm of spongiosa was removed from the distal articular surface of the femur whereby a new articular surface arose. The course of regeneration was studied by means of planimetry and injection of Indian ink on the 7th, 20th, 26th, 33rd, and 70th days, to establish the relationships of cartilage formation and vascularization in the granulation tissue covering the articular sur-

face. The granulation tissue was found gradually to lose its vessels. This process appeared in spots, and at these spots was cartilage formed.

Owing to the constriction and obliteration of vessels, the oxygen supply of the tissues becomes insufficient. Determinations by Wong's method have shown the haemoglobin content of the granulation tissue gradually to decrease in the course of the regeneration process.

Oxygen deficiency was expected to lead to an increase of the lactic acid content in granulation tissue. As determined according to FRIEDMANN, COTONIO and SCHAFFER and to BARKER and SUMMERSON, the amount of lactic acid displayed a gradual increase until the 26th day, after which time it diminished markedly. The onset of the decrease coincided with the formation of the first cartilage islets.

The respiratory enzyme system of granulation tissue was examined in Warburg's apparatus, in a Krebs—Ringer-phosphate medium, at 37° C. It has been found that respiration could have taken place with increasing intensity until the 33rd day ; subsequently, respiratory capacity diminished considerably.

From the above data it has been concluded that the relative hypoxia ensuing locally might be a factor promoting cartilage formation.

Enhancement of the Streptomycin Effect by Influencing the Inner Environment

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Considering that streptomycin does not pass through the wall of living cells, nor into encapsulated areas, it cannot act on intracellular or encapsulated bacteria. Augmenting the diffusibility of the drug would therefore be of considerable importance. Such an effect may be expected from histamine. On this basis was histamine administered together with streptomycin to 16 guinea pigs. Streptomycin treatment, started 4 to 5 weeks after infection with doses of 20 mg/kg body weight, administered every second day for 3 months, was more effective if histamine was also administered (0.2 mg/kg, subcutaneously, 1 1/2 hrs. after injecting the streptomycin). The animals treated with both drugs lived longer than the controls. In another series, consisting of 24 animals, the combined treatment was begun 4 weeks after infection and was followed for 6 weeks. 2 weeks after the last injection the animals subjected to combined treatment exhibited less severe tuberculosis than the controls. In other experiments, hyaluronidase acted like histamine. The conclusion seems justified that histamine acts by its spreading effect. The deleterious action of histamine on human and animal tuberculosis is apparently counteracted by streptomycin, whereby its advantageous effect, *i. e.* that increasing diffusibility, becomes manifest.

Developmental Histochemistry of the Myoneural Junction (Cholinesterase Activity and Sulfhydryl Reaction)

B. Csillik, Gy. Sávay

(Dept. of Anatomy, Medical University, Szeged)

Development of the subneural apparatuses of motor end plates has been studied in rats by means of the Gerebtzoff acetylthiocholine method (cholinesterase) and by means of the authors' "lead reaction" (for demonstration of sulfhydryl groups). Both reactions occured in identical structures. Within the primitive "Anlagen" of skeletal muscles, both reactions appeared in the cytoplasm of interstitial cells ("teloblasts"). In the first period of development the nuclei of these cells are surrounded by reactive halos, later the reactions become evenly distributed in their expanding cytoplasm. In the next period enzymic activity and —SH reaction increases in some points of the cytoplasm, while the nucleus has been pushed to the cell margin. After a time, vacuoles appear in the cytoplasm of these „teloblast" cells, thus

producing a primitive form of the subneural apparatus. In the course of the third postnatal week some interstitial cells abandon the neural bond. Reactivity of these emigrated cells decreases and granula displaying metachromasia appear in their cytoplasm.

Considering that the participation of active —SH groups in the molecular structure of Coenzyme-A is a well-known fact, the identity of the respective histochemical patterns of cholinesterase and of sulfhydryl reaction suggests that both systems, — the one synthesizing acetylcholine and the other hydrolysing it — are located in identical cellular structures even since the very first phases of ontogenesis.

On the Innervation of Smooth Muscles

Márta Kozma, A. Gellért, J. Lippai, Mária Poberai

(Dept. of Anatomy and Embryology, Medical University, Szeged)

The innervation of smooth muscles has been investigated in the organs of domestic animals by vital and supravital methylene blue stain and silver impregnation.

Both the methylene blue and the protargol specimens showed a terminal plexus, the fine fibres of which ramified among the smooth muscle cells. The density of the plexus is different in various organs, their relation to the smooth muscles is, however, the same.

In its course the fibre mostly becomes tightly adjacent to a smooth muscle cell, or to two or three, then it joins a thicker plexus, or it cannot be traced at all.

In a few cases the areas of the smooth muscle cells, to which the terminal fibres were attached, displayed cholinesterase activity.

In smooth muscle neither structures resembling nerve endings, nor the individual innervation of each smooth muscle cell could be demonstrated. All preparations exhibited an innervation pattern characteristic of a vegetative, plexiform innervation. Peripheral innervation is performed by fine fibres detaching from the ground plexus and coming in close contact with the smooth muscle. The places of contact are presumably those which display enzymatic activity, wherefore these may be considered the sites of synapses.

Submicroscopical Morphology of the Perineurium

P. Röhlich

(Dept. of Histology and Embryology, Medical University, Budapest)

The fine structure of the perineurium was examined in rats by polarization and electron microscopy. The perineurium is 1 to 1.5 micron thick. Its anisotropy is made up of three components, a positive form, a positive intrinsic and a negative intrinsic birefringence. As the latter disappears on treatment with lipid solvents, it presumably originates from lipid molecules arranged vertically to the surface of the perineurium, whilst the first and the second are due to fibres or lamellae parallel to the plane of the perineurium.

Electron microscopy has corroborated this hypothesis, revealing that the perineurium is composed of 5 to 6 thin, entirely closed cell layers. Each layer is about 0.1 micron thick, *i. e.* at the limit of the dissolving power of the light microscope. In the cells, nuclei, mitochondria endoplasmic reticulum, Palade's granules, phagocyted particles could be distinguished. The cell membrane displayed peculiar invaginations, presumably identical with the so-called pinocytotic vacuoles. The cell layers are covered on both sides with a homogeneous basement membrane, 18—20 millimicrons in thickness. Between the cell layers there are connective tissue fibrils running parallel to the axis of the nerve. They probably correspond to the argentaffine fibres of the perineurium.

The fine structure of the perineurium explains its being a diffusion barrier, a function observed in previous experiments. The above data may be useful in investigations into the electrophysiology and pathology of the peripheral nerve.

Examination of the Functional Reactivity of Rat Thyroid Homografts by Measuring I^{131} Uptake and by Histometry

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In a previous study, homotransplantation of rat thyroid was described and morphologic evidence of its success was presented. In the present series, the function of the grafts was examined as to the capacity of I^{131} binding and the height of thyroid epithelium.

The graft becomes active after the removal of the host's thyroid. The increase in I^{131} uptake started on the 11th day. The height of the epithelium as early as one day after thyroidectomy displayed a statistically significant difference in comparison with the controls. The increase in cell height continues until the 10th day, then the height becomes constant.

Thus, the grafts react within hours to the increased TSH production induced by thyroidectomy. Their ready response to the mild endogenous TSH-stimulus shows that their functional value for the host practically attains that of the normal thyroid.

Homoiotopical Transplantation of Rat Ovary

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Ovarial auto- and homografts were implanted to the site of the removed ovary. Successful transplantation was assumed if Allen-Doisy's test was positive or if pregnancy had ensued. Autotransplanted ovaries adhered and functioned. Homografts in untreated hosts, on the other hand, were partly destroyed, partly became inflamed. On treatment with an adaptation dose of cortisone, some grafts remained intact, while others displayed mild inflammation, but none was destroyed. It has been concluded that cortisone treatment inhibits the host's immunologic processes which usually destroy the ovarial homografts.

Contributions to the Development of Bursae

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The development of bursae has been studied, the pertinent literary data being controversial. The subject of the study was the development of artificial bursae, and the formation of mechanism of the prepatellar bursa from embryos of different age. Under experimental conditions, a space with a connective tissue wall had formed between the implanted bone segment and the muscle tendon, resp. the cutis. In fresh experimental and subcutaneous bursae, cellular infiltration is present which, however, may have been due to inflammation. Pronounced degenerative phenomena were not observed. Subtendineous bursae have their own wall of connective tissue, without an epithelial or endothelial lining. The subtendineous bursa with its own connective tissue wall appears in the 4th month of intrauterine life. The picture seen in preformed subcutaneous bursae seems to confirm Virchow's theory on primary connective tissue atrophy.

SECTIONAL MEETING

II. Pathology

Lung Segments in Domestic Mammals

E. Guzsal

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The topography of the lung segments can be established in animals like in man. The lungs of different animals being of a different shape, segments also differ regarding shape, size and number. Human lungs and lungs of domestic animals may be considered homologous organs, although certain animal species display characteristic features in the lobulation of lungs and the formation of the bronchial tree. As to bronchial branching, in animals the monopodic type, in man the dichotomic type prevails. The accessory lobe belonging in animals to the right lung is no separate lobe in man, but one segment of the right and one of the left lung correspond to this area (segmentum basale mediale dextrum et sinistrum). As to structure of the bronchial tree, the bronchus of the right apical lobe has a characteristic feature in ruminants and swine, it being a tracheal bronchus branching off the laryngeal tube high above the bifurcation.

The segments of the human lung may be regarded as bronchoarterial units, because by the veins passing intersegmentally two or three segments are drained. In domestic animals there are also segments of the bronchovascular type, because both the arteries and the veins are located intersegmentally. As to the number of segments, in domestic animals more segments can be defined than in man, especially in the diaphragmatic area, in which there are more dorsal segments. Segments have been termed in accordance with the nomenclature used in veterinary medicine. (F. i.: Segm. apicale ventrale.)

Up to date, few papers dealing with the anatomy of animals have been concerned with the pulmonary segments, but once attention has been directed to their significance, the knowledge of the detailed structure of the lung will make a great progress in veterinary medicine.

Lungworm Disease in Cattle

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Pulmonary infestation of cattle with D. viviparus is widespread in some regions of Hungary and the economic loss caused by the disease is at times considerable. The present examinations were carried out in 13 bovines about 1 year old, infestation of which with D. viviparus had taken place under natural conditions. Of the histologic changes, epithelialization of the alveolar lining, ingrowth of the bronchiolar epithelium into the bronchiolar cavities, and hyperplasia of the lymphoid tissue surrounding the bronchioli, were observed within the affected lobules.

In addition, there were hyperplasia of smooth muscle elements in the bronchial and bronchiolar wall, degeneration of peribronchial ganglion cell groups, elastosis of elastic fibres in the wall of the air passages of the lung, then the dissolution of elastic elements, and basocellular metaplasia of ciliated epithelium, changes that previously had not been observed in pulmonary helminthiasis.

Lungworm disease of cattle in the patent stage and after the disappearance of worms corresponds histologically to a specific type of bronchopneumonia, characterized by exsudative

and desquamative processes in addition to atelectasis, epithelial changes, elastosis of elastic elements in the alveolar walls. The aforementioned changes occur in the respiratory pathways.

The pulmonary process does not cease after the worms have left the lungs. The inflammation assumes an interstitial character which ultimately results, in the atrophy of lung parenchyma.

Morphologically, the condition resembles the tumour-induced pneumonia of man. The process has been termed obstruction pneumonitis by MACDONALD et al., and LÜDEKE. Its main feature is atelectasis with hypersecretion in the air passages. The secretion cannot be expectorated on account of the obstruction, it streams backward, becomes engorged in the small airways and may fill the alveoli. The mucous secretion, not being absorbed from the alveoli, undergoes organization partly under bacterial action, then it becomes indurated. The emptying of secretion may be impeded also by the worms obturating the air passages. Therefore, the genesis of the two processes is similar.

Changes of the Myocardial Fibres in Pulmonary Thromboembolism

S. Ökrös

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The myocardium of some subjects who had died of pulmonary thromboembolism was histologically examined. The cross striation displayed a considerable change in the area of the right ventricle : band Q was attenuated to one fourth, band *I* was broadened to fourfold of its original size. In addition, torn muscle bundles resp. fibres were found, especially below the endocardium, as in vital lesions. In the muscle fibres of the left ventricle the cross striation was unchanged, band Q and *I* were identical in breadth.

The observed changes may have arisen in consequence of the sudden strain exerted on the right ventricle by pulmonary embolism.

Incidence of Fulminant Pulmonary Embolism

J. Juhász, G. Gyenes

(1st Dept. of Pathology and Experimental Cancer Research, Medical University, Budapest)

Authors studied the cases of fulminant pulmonary embolism revealed by necropsy in the period from 1938 to 1957 in individuals beyond twenty years of age. The total number of cases was 211 (3.5%). During World War II the number of embolisms was considerably reduced, after the war it became again more frequent, especially in the sixth decade. Women were afflicted twice more frequently than men.

Embolism attending internal diseases, postoperative embolism, venous thrombosis, relationships of pulmonary infarction and fulminant embolism, relation of the nutritional condition to pulmonary embolism, have been discussed in detail. In the last ten years, fulminant embolism was increasing in frequency both in men and women. Patients suffering from cardiovascular disease or malignant tumour were most frequently affected by lethal pulmonary embolism. The clinical diagnosis of fulminant embolism had been found to be erroneous in 51% of the postoperative and in 70% the internal cases.

Contributions to the Histopathogenesis of Gout

D. Tanka

(State Institute of Rheumatology and Medical Hydrology, Budapest)

Aetiology and pathogenesis of gout are still unknown. Attention has been focussed to the disorders of nucleinic acid metabolism ; the role of tissue factors has been neglected. Ebstein's theory on necrosis and subsequent precipitation of uric acid has not been proved. UMBER and GUDZENT attributed some role to allergic factors, without, however, substantiating their assumption.

We have found that the granulation tissue surrounding uric acid deposits contained Schiff-positive giant and other cells. The connective tissue displayed metachromasia. The changes resemble those appearing in allergic, rheumatic alterations of the joints. The precipitation of uric acid is probably preceded by colloid changes in the tissue. A special alteration of the basic substance of joints, along with other pathogenic factors, is assumed to have a role in the development of uric arthritis.

Histologic Studies in Artificial Hibernation

I. Betléri, D. Tanka, K. Farkas

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Lytic cocktail (chlorpromazine, promethazine and pethidine) was administered to guinea pigs and rabbits, and the animals were cooled to different temperatures (30°, 26°, 24°, 22°, 20°, 18° C) and then sacrificed. The most conspicuous histological changes were found in the liver. At 30° C moderate congestion, an uneven wasting of Schiff-positive granules in the cytoplasm, and appearance of larger granules was observed. At 26° C this phenomenon was more pronounced, large areas were entirely devoid of granulation. At 24° C centrolobular fatty degeneration ; at 22° C, swelling of liver cells occurred. At 20° C and 18°, necrosed foci appeared, the epithelium of the convoluted tubules was swollen, in places the lumen had disappeared.

These changes were more pronounced in the organs of animals which had responded to cooling with excitation. They were, however, present also when artificial hibernation was successfully carried out. On the basis of the observations it is claimed that hibernotherapy is by no means indifferent to the parenchymal organs. The adrenergic counterregulatory mechanism released by cooling should be blocked and liver function should be supported by infusions of dextrose (laevulose) and other drugs.

The Action of Metal Ions on the Nucleic Acids of Cell Nuclei under Normal and Pathologic Conditions

K. Jobst

(Dept. of Pathology, Medical University, Pécs)

If nucleic acids are exposed to acid hydrolysis, the purine rings are split off and apurinic acid accessible to ribonuclease is formed. From the fact that apurinic acid is digested by ribonuclease several authors have inferred a structural similarity between apurinic acid and ribonucleic acid. — When examining the action of metal ions, namely lanthanum and cerium, on the molecule of apurinic acid by anisotropic staining and polarization microscopy, we found that this compound was depolymerized by these metal ions. Thus the depolymerization of apurinic acid by ribonuclease is not due to a specific action of this enzyme.

Furthermore the depolymerization of DNS and apurinic acid induced by various metal ions has been studied quantitatively on normal and pathologic nuclei by a polarization microscopic method.

Osteoplastic Pneumopathy

L. Nagy, K. Stekker

(2nd Dept. of Pathology, 1st Dept. of Internal Medicine, Medical University, Budapest)

Osteoplastic pneumopathy is a rare disease, appearing in two different patterns, depending on whether the shape of bone formed is nodous or branching.

A case belonging to the second group has been observed. Bone formation was most pronounced in the inferior lobes, it surrounded some vessels, and was covered by an amyloid coat. No other organ revealed bone formation. Amyloid was, aside from the lungs, found also in the gastric wall, where the amyloid clumps were partly calcified. It is thought that the formation of normal bone tissue in the lungs has been favoured by their active motion.

Palaeopathologic Investigations of Egyptian Mummies from the Roman Period

Gy. Mérei, J. Nemeskéri

(2nd Dept. of Pathology, Medical University, Budapest, and Anthropologic Dept. of the National Museum, Budapest)

The skulls of 25 mummies from the Roman period found in the Delta, have been studied. First, the method was examined, how the brain had been removed before embalming. According to the two methods of embalming described by Egyptian Papyri and Greek authors, the brain was removed through the nose or the foramen magnum. The latter procedure was less expensive : the head was severed and, after emptying, was fixed at its place by means of threads and a rod applied into the spinal canal. Both methods of removing the brain could be traced in the present material. In several skulls, during the transnasal procedure the paranasal (including the sphenoidal) sinuses had been opened up. This is the more remarkable as by Grapow's philologic analysis it has been demonstrated that the Egyptians did not know of the existence of paranasal sinuses. On the mummy of a man aged 40 years, the foramen jugulare was considerably obstructed by an osseous growth. This is an anomaly which by the sudden increase of intracranial pressure may lead to death. Another skull displayed wooden nasal prothesis. This had evidently been applied after death, because the thread holding it was introduced above the closed mouth and knotted on the cranial basis. The old Egyptians believed that body, Ka-"soul" and Ba-"soul" constitute a close union, the dead would join Osiris in the other world. It is for this reason that the deficient nose had to be replaced. This prothesis found on a mummy is an unique finding.

Developmental Anomalies of the Urogenital Apparatus and the Intestines

Magda Scholz, A. Mészáros

(2nd Dept. of Pathology, Medical University, Budapest)

After a review of the pertinent studies, two own cases have been reported. No similar combination of malformations was found in the literature.

In a 7-month-old male infant anal atresia, partial atresia of the rectum, rectovesical fistula, patent foramen ovale, cryptorchism, and pes equinovarus on the left side were present. One kidney was missing, there was a secondary rudimentary kidney, and no gall bladder.

A male newborn 6 days of age had neither a rectum nor a sigmoid, the renals were rudimentary and so were the ureteric bundles. Further, the urinary bladder and the urethra were atresic, and the prostate was missing. No such exogenous factor as would have accounted for the anomalies was detected in the history and their appearance is explained by a developmental mechanism.

Developmental Anomalies of the Heart

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(2nd Dept. of Pathology, Medical University, Budapest)

From 1949 to 1958, 4800 necropsies were carried out, among them on 1309 children under 15 years of age. In 117 cases was a grave malformation of the heart observed. These were evaluated statistically and now a review of the pertaining literature has been given. Open foramen ovale was observed in 257 cases, so that the data according to which this anomaly would occur in 20 to 30 per cent of adult persons could not be confirmed. Similarly, the aetiologic factors which are usually made responsible for cardiac malformations have not been met with in the present material ; in the cases in question, rubella or other viral diseases had not occurred in the first three months of pregnancy with a conspicuous frequency, neither had bleedings or inherited factors. Ten cases of malformation could not be allotted to any of the statistical groups, neither could their development be interpreted on the basis of the known theories.

Mechanism of Conduction Disturbances in Hypertension

Sz. Virágh, Julia Kiss

(Dept. of Pathology, Medical University, Szeged)

Twentyfive hearts were examined. Of 17 cases in which there had been hypertension, electrocardiography had revealed absolute arrhythmia in 12 ; of the 17 cases there were two right, and two left bundle-branch block. One of the former had been associated with a WPW syndrome. As a control, 8 hearts were selected from corresponding age groups.

The structures in question were cut up according to the authors' own method and that suggested by LEV. From each case 70 to 200 sections were prepared. Crossmon's trichrome stain, acid fuchsin + toluidine blue for the determination of the isoelectric point, and staining with Sudan were found the most sensitive methods for the demonstration of specific myocardial lesions.

According to the findings, the conduction system is more frequently damaged by slow necrobiotic than by rapid necrotic processes. The alteration of the sinus node is influenced mainly by the condition of small vessels and the interstitial connective tissue. The lesions of Tawara's node and the bundle branches are due to vascular, environmental, mechanical, and dilating factors. Only advanced cases seem to be recognizable by clinical examinations. It was always possible to determine the structural change which during life had been responsible for the electrocardiographic alterations.

Effect of Adrenaline on the Rabbit Kidney

Edith Beregi, L. Haranghy, I. Földes

(2nd Dept. of Pathology, Medical University, Budapest, and National "Korányi" Tuberculosis Institute, Budapest)

In earlier experiments the authors had induced by pilocarpine administration and cool bath acute and subacute diffuse glomerulonephritis in rabbits sensitized to horse serum. In the present examinations it has been studied whether the mobilization of adrenaline induced by pilocarpine were playing a role in the development of glomerulonephritis. Two experimental series have been carried out.

(i) Glomerulonephritis was produced by above method after bilateral adrenalectomy. The operation had no influence on the course of the renal process.

(ii) In rabbits sensitized to horse serum, treatment with adrenaline and cool bath sclerosis was observed to develop in the renal arterioles and prearterioles. If the animals had been treated with adrenaline without cool bath and previous sensitization, the vascular change was similar but milder.

Liver Changes in Shock

A. Haraszti, P. Endes

(Dept. of Pathology, Medical University, Debrecen)

The liver was examined in 21 cases where death had ensued with symptoms of shock. Degeneration characterized by the appearance of vacuoles, protein droplets, and fat, further necrosis, chiefly central, and congested sinusoids were found. For the changes, hypoxia has been made responsible and it is thought that the severity of hypoxia was a more important factor, than its duration. The gravest cases displayed central blood pools in the liver and signs of shock in the kidneys. Experimental histotoxic hypoxia elicited by insulin produces a histologic pattern different from that of human stagnation hypoxia.

Microscopic Studies in Fatal Cases of Shock

I. Gy. Fazekas

(Dept. of Forensic Medicine, Medical University, Szeged)

It is well-known that in animals died with shock, bronchial spasm, spasm of the pulmonary and hepatic vessels, pulmonary and cerebral oedema are found post mortem. The morphologic signs of lethal shock in man have not been described.

Microscopic examination of organs of subjects who had died from shock due to operation, injury, burns, scalding, poisoning, entering of X-ray contrast material into the circulation, abdominal haemorrhage, blood loss, etc., revealed certain constant changes. These were, detachment of the intimal cells ; accumulation of dark granules in the endothelial cells, vessel walls, leucocytes ; granular fragmentation of endothelial cells and leucocytes ; excessive dilatation and engorgement by plasma or erythrocytes of the hepatic capillaries ; disintegration and fragmentation of liver cell columns ; occasional microscopical haemorrhages in lungs and liver parenchyma ; the presence of liver cells in the central or the hepatic veins (liver cell mobilization) as the most constant sign ; frequently, the spasm of hepatic arteries ; pulmonary oedema ; infrequently, bronchial spasm ; spasm of pulmonary vessels ; liver cell emboli in the pulmonary capillaries or the presence of liver cells in the alveoli ; and cerebral oedema in all cases.

The simultaneous presence of these changes represents the histologic evidence of humans from shock in death, especially characteristic is the mobilization of liver cells, a sign which was invariably present in shock-death but was missing in the controls who had died from other causes. The mobilization of liver cells is a sequel of the excessive dilatation of hepatic capillaries, their engorgement with serum or blood, whereby a mechanical effect is exerted on the liver cells and the capillaries. In this way may be explained the lesion of capillary walls and the disintegration of liver parenchyma.

The simultaneous presence of the changes described allows the diagnosis of shock-induced death in man. Further, these signs make it possible to distinguish between death-shock due to during operation and death due to an overdosage of anaesthetics. In the latter case neither liver cell mobilisation nor the other cellular lesions are present.

Pathology of Diffuse Progressive Interstitial Pulmonary Fibrosis (Hamman-Rich Syndrome)

I. Kiss

(City Hospital, Tétényi Street, Budapest)

Clinical and pathological observations have been made in two cases of diffus pulmonary fibrosis running an acute course. To date, about 50 similar cases have been published in the literature. As a rule, no correct diagnosis can be established during life. In most cases, the condition takes an acute course during which nodular fibrosis develops, extending nearly over the entire lung. Under the microscope, signs of rapid progression are seen ; the epithelium of the remaining alveoli becomes cubic. The aetiology of the disease is unknown ; authors believe it to represent the final stage of atypical primary pneumonia.

On Haemochromatosis

G. Bőcs, I. Besznyák

(1st Dept. of Pathology and Experimental Cancer Research, Medical University, Budapest)

After a review of the literature and the theories of pathogenesis, the theory of KRAININ and KAHN has been discussed, according to which the condition in question would be due to a disturbance of the enzyme system achieving the combination of iron and ferritin.

On the basis of data in the literature, the physical and chemical properties of the pigments occurring in bronzed diabetes have been discussed, especially their staining, incidence, and their interrelations with ceroid, vitamin E deficiency pigment, and lipofuscin.

A case has also been reported, along with the clinical features of haemochromatosis, with due regard to the frequently concomitant diabetes. The dominance in males and the facultative character of dermal pigmentation have been emphasized. In the case reported dermal pigmentation was missing, but there was a remarkably extensive storage of iron pigment in endocrine organs (pancreas, thyroid, parathyroids, adrenals, testicles, pituitary).

Primary Systemic Amyloidosis

Gy. Gorácz, Gy. Szinay

(2nd Dept. of Pathology, Medical University, Budapest)

After discussing the clinical and pathological features of primary systemic amyloidosis a case has been reported in detail.

The patient had for 10 years been treated for lymphogranulomatosis with X-ray irradiations and nitrogen mustard derivatives. Post mortem no sign of lymphogranulomatosis was found. Instead of this, there were extensive amyloid precipitations of unusual location (heart, lungs, salivary glands, thyroid, skin, intestinal wall, skeletal muscles, sciatic nerve, etc.), further at the typical sites of amyloidosis (spleen, adrenals, small vessels, etc.). In the skeletal muscles and the myocardium there was infiltrative inflammation.

As to the aetiology, polymyositis and the chronic administration of nitrogen mustards had to be taken into consideration.

Pulmonary Arteritis Induced by the Intravenous Administration of a Synthetic Polymer

Éva Horváth, K. Kovács, V. Balázs, Margit Fröhlich, S. Benkő

(Dept. of Pathology and 1st Dept. of Internal Medicine, Medical University, Szeged)

The effect of intravenously administered methyl cellulose (molecular weight, 80.000) on the vessels of dogs has been studied. Of the 1 per cent solution of the compound, 20 ml doses were injected twice every week for 5 months. In the lungs of the animals marked arteritis in the small and medium-sized arteries was found, often attended by fibrosis and perivasculitis. The most conspicuous change was a proliferation of the intima into the lumen ; this proliferation was partly symmetrical, partly bulbous, it was made up of foamy cells storing methyl cellulose, and sometimes it filled the lumen of the considerably dilated vessel. In numerous places the substance was stored under the intima. Beside these vascular lesions, numerous storing granulomas were present in the interstitium.

Simultaneous laboratory examinations revealed intensive and lasting hypercholesterolaemia, and hyperlipoproteinaemia.

It is thought that the changes observed were due partly to a direct action of the methyl cellulose and partly to its indirect effect enhancing lipid transport.

SECTIONAL MEETING

III. Forensic Medicine

Incidence of Suicide in 32 Years' Necropsy Material

F. Bartos

(Dept. of Forensic Medicine, Medical University, Szeged)

The cases of suicide in 32 years' necropsy material have been examined as to age ; sex ; constitution ; seasonal incidence ; time of the day and the mode of suicide ; correlations between menstruation and suicide ; acute and chronic diseases.

Among 4449 deaths, 814 were due to suicide (18.3%), 488 were men (59.95%), 326 were women (40.05%). The constitution was asthenic in 450 (55.2%), pyknic in 188 (23%), athletic in 176 (21.8%) cases.

Suicide was committed in summer by 248 (30.41%), in spring by 211 (25.92%), in winter by 207 (25.4%), in autum by 148 (18.28%) individuals. As regards the time of the day, cases committed in the forenoon prevailed.

As to age groups, the greatest number (171 + 21%) were from 15 to 25 years old. The lowest number was found among those aged from 75 to 85 years (35 + 4.5%). In the other age groups there were no conspicuous differences. 118 (36.1%) of the 326 women committed suicide during menstruation.

The causes of suicide were in their order of frequency : economic difficulties ; mental disease ; extramatrimonial pregnancy ; incurable disease ; jealousy ; chronic alcoholism ; bad marks in school certificate ; first love ; fright of penalty ; parents' harshness ; intolerable solitude ; exhaustion ; sterility.

The Reflexion of the Laboratory Evidence of the Influence of Alcohol in the Sentences of the Courts

R. Budvári, V. Földes

(Criminal Investigating Laboratory, Budapest)

In a previous lecture the practical evaluation of blood alcohol estimations in cases of road accident was reported. In the present report has been discussed the role of alcohol in other criminal acts, *e. g.* assault on officers of the law, ruffianism, sexual offences, etc. together with the pertaining decision of the courts. While the role of alcohol in road accidents being jugded on a more or less uniform pattern, in other criminal acts the correct estimation of the alcohol effect constitutes an intricate problem.

Ethanol Poisoning in Children

T. Kaszás, J. Nagy

(Dept. of Paediatrics and Dept. of Forensic Medicine, Medical University Debrecen)

In 10 years, 24 cases of alcohol poisoning were admitted to the paediatric department. One of them was lethal; an 8-years-old girl died with lesions of the central nervous system 20 days she had ingested 70 g of 96% ethyl alcohol.

The problems of differential diagnosis have been discussed together with the importance of alcohol determination in blood, urine, and CSF. These examinations should be carried out

in the early phase of poisoning, because later a negative result does not rule out the alcoholic aetiology of the severe condition. In lethal cases, microscopic examination of liver and brain may furnish evidence of a toxic damage, though the alterations are not specific. Finally, the importance of prevention has been emphasized.

Histologic Changes in the Central Nervous System in Cases of Survived Hanging

E. Somogyi, V. Fáber

(Dept. of Forensic Medicine, Medical University, Budapest)

After a four-day survival of hanging, authors examined the changes in the central nervous system. The rope was cut 3 or 4 minutes after the self-hanging and the suicide was transported into a hospital. He was unconscious until death, which was due to pneumonia. Microscopically, in the brain swollen cells, at places shrunken cells, granulation in the plasma, tigroid clumps, circumscribed numerical decrease of ganglion cells, shadows intravasal leucocytosis have been observed.

Significance of Fat Embolism in Injuries

E. Kelemen

(Court of Justice, Budapest)

It has been observed in numerous cases that not only bone injuries, but nearly all kinds of injury to soft parts are associated with fat embolism. This manifests itself especially with a marked interference with pulmonary circulation.

Fat Embolism Following a Shot Wound of the Abdomen

Gy. Dallos

(Central Hospital of the Hungarian Army, Budapest)

A shot wound penetrating the abdomen was followed by fat embolism. According to the literature, fatal fat embolism rarely ensues in such cases. In the present instance, the embolus was obviously released from the fatty abdominal wall, but the subsequent operation might also have had a role. The less frequent causes of fat embolism have been discussed. In similar cases, surgical management should take place most carefully, although complications sometimes cannot be prevented despite an utmost care at operation.

A Rapid Micromethod for the Detection of Nicotine

Klára Zsigmond, J. Nagy

(Dept. of Forensic Medicine, Medical University, Debrecen)

A rapid semiquantitative method for the determination of nicotine has been presented. After alkoholization the sample is subjected to a simple distillation process and the distillate is received in a hydrochloric medium. A dilution series is then prepared of the distillate and the nicotine is precipitated with silicotungstic acid.

For the determination, a special apparatus has been designed. This consists of a 120 ml distilling flask, a ground glass attachment, and a receving vessel. The attachment consists of a three-stage foam-trap, in which are mounted a foam-depressing filter and a three way vapour head, through which the nicotine bearing vapours escape. To the top of the column a bent glass pipe is fitted, the vertical leg of which extends downwards into the receiving vessel. The precise dimensions of the apparatus are presented ; a close adhering to these is important because they influence the amount of nicotine distilling over.

From the sensitivity of the silicotungstic acid reaction, the amount of the original sample, and the fact that only 80 per cent of the nicotine present is assayed, the nicotine content of the sample is quantitatively determined by computation.

Alcohol Sound

Klára Zsigmond, J. Nagy

(Dept. of Forensic Medicire, Medical University, Debrecen)

The otherwise stable solution of ammonium bichromate in sulphuric acid is readily reduced by alcohol, even at room temperature, and then the yellow colour of the solution turns into green.

This makes it possible to apply the reaction for demonstrating alcohol in the expired air. The reagent is dissipated on glass particles, to enlarge its surface. The glass particles moistened with the reagent are placed in a glass tube so narrow as to secure the immobility of the granules. The amount of air streaming through the tube is measured by means of blue gel. When alcohol is present, the described colour change ensues.

The apparatus permits quick information. Being of the size of a fountain pen and easy to handle, it suits itself well for tests made by lay authorities.

(At the session, the photographs of the apparatus and its function have been presented.)

Electric Hand Dryer

L. Pusztai

(Dept. of Forensic Medicine, Medical University, Debrecen)

An apparatus for drying hands has been devised. Streaming hot air is supplied by a ventilator working behind an electric heater. The whole apparatus can be mounted on a wall or a stand, and set in function by a foot switch. It should be used in necropsy rooms and other places where infectious material is handled.

(Drawings and slides are shown.)

Portable Necropsy Table

L. Pusztai, J. Nagy

(Dept. of Forensic Medicine, Medical University, Debrecen)

The portable necropsy table shown is made of aluminium and weighs 14 kg. It can be folded to a suitcase shape, and the necessary equipments (instruments etc.) are placed in it. All its parts can be cleansed or sterilized. It is useful if necropsy has to be performed in remote places. (Drawings and slides are presented.)

Specific Demonstration of Traces of Human Blood on the Basis of the Fibrinolytic Enzyme System

E. Szőllősy, B. Rengei

(Dept. of Microbiology and Dept. of Forensic Medicine, Medical University, Szeged)

Blood contains a fibrinolytic enzyme system which is normally inactive. Under certain conditions it may, however, become activated in the organism, while *in vitro* it is activated by chloroform, tissue extracts, filtrates of certain bacteria, etc.

Streptokinase from the filtrate of haemolytic streptococci exerts a specific effect on the fibrinolytic enzyme system of human blood. This specific effect is based on the activation of the so-called human factor, a proactivator, which is present in human blood as a constituent of the fibrinolytic system. As to the details, the comprehensive work of MÜLLERTZ should be consulted.

A method has been worked out for the demonstration of traces of human blood. The fibrinolytic system is demonstrated by the application of fibrin plates procured from cattle plasma. The blood patch is extracted with 2 ml of a physiologic sodium chloride solution containing Veronal buffer (m/100, pH 7.6). The buffered saline contains 250 gamma Streptokinase (Distreptase, Warszawska Wytwornia Surowic i Szczepionek). Droplets of the extract 0.02 ml each are allowed to fall upon the fibrin plate, which is then incubated at 37° C for 8 hours. To prevent the growth of bacteria, the fibrin plate contains 40 mg sulfamethylthiazole per each 100 ml. Activation of the sytem is assumed if fibrinolysis extends to a circle 10 mm in diameter. Patches of human blood that had dried on various objects (iron, glass, textile) and had been kept at room temperature for 8 months, still yielded a marked reaction. Samples kept at 56° C for 10 days also reacted positively. Blood was demonstrated also on a piece of linen which after contamination had been washed with soap at 70° C so that the blood was not visible. The washed linen gave a positive reaction as late as two months after drying. All controls (traces of blood of domestic animals, poultry, etc. treated in a similar manner) were negative. Human tear and mother's milk give a weak reaction.

The serologic identification of traces of human blood is associated with difficulties and sources of error, The demonstration of human blood by means of the fibrinolytic enzyme system may be regarded as a completion of forensic serology. Pertinent studies are in progress.

Mycological Report of an Exhumated Corpse 50 Days After Death

A. Dósa

(Dept. of Forensic Medicine, Medical University, Szeged)

Between 1947 and 1950, 20 corpses were exhumed in the environment of Szeged. Correlations were found between the time elapsing from burial to exhumation and the infestation of the cadaver by fungi. The forensic significance of such correlations consists in that the fungi found in an unknown corpse allow some conclusions as to the time of death. The number of examinations performed did not allow to draw definite conclusions. The present examinations were carried out to collect further data.

A man 78 years of age had died suddenly on February 7, 1958. He had beer buried next day. 50 days later the corpse was exhumed because of suspected poisoning. A thick, abundantly growing, white mould covered the face, neck, right forearm, left elbow, both inguinal regions, and the anterior surface of the penis. On the scalp, hands, posterior crural surfaces, the buttocks, and along the spine, a thick bluish-gren coat of mould was seen. The white mould consisted of Cephalosporium acremonium Corda, the bluish one was produced by Penicilin glaucum. The latter finding corresponds to our earlier results, when the same fungi had been demonstrated on 14 cadavers 1 to 3 years after burial.

Cephalosporium acremonium Corda, the fungus now present 50 days after burial, was earlier found in one case only, on a body that had been buried 4 years before exhumation.

The ground was dry sandy clay. The body was emaciated. The coffin was intact, in a depth of 180 cm. The fungi exhibited a strikingly abundant growth. The soil contained none of these fungi, and it is assummed that they had found their way into the coffin with the clothes.

Living Infant Attacked by Animal

L. Takácsy, O. Szűcs

(Dept. of Forensic Medicine, Medical University, Budapest)

Living persons are rarely attacked by animals. As a rule, the victims are infants, or adults incapable of protecting themselves. The aggressor may be a dog, domesticated wolf, rat, etc. Domestic cats are rarely mentioned. In the reported case an infant 7 months of age had been left alone in a closed room on a farm. When coming home and opening the door, the mother saw their cat to jump off the lacerated bloody face of the infant. The cat's face was smeared with fresh blood. The child died within a few hours.

Necropsy of the infant revealed on the soft parths of the mouth, nose and the upper jaw defects characteristic of cat bite. The lungs contained aspirated blood. the stomach contained blood with particles of the maxilla and from the teeth buds.

Death was due to blood loss and shock.

The cat must have been very hungry. The smell of milk coming from the infant may have caused the excitation resulting in the attack.

Conjunctival and Corneal Lesions Due to Calcium Salts

K. Gát, J. Nagy

Dept. of Tuberculosis and Department of Forensic Medicine,
Medical University, Debrecen)

A girl 17 years of age had put a small piece of mortar in her conjunctival sac, in order to bring about inflammation and corneal ulcers and so to get sickness benefit. She was on sick pay for almost two years.

Histology revealed in the excised conjunctival sample lime granules and chronic inflammation with slight cellular infiltration. Experiments were made to reproduce the process in animals. By the administration of calcium carbide or calcium carbonate into the conjunctival sac of rabbits, lesions were induced which on both gross and microscopical examination resembled the changes displayed by the patient.

The conclusion has been drawn that in cases of conjunctival and corneal changes of unknown aetiology, calcium compounds as causal factors should also be thought of.

Differential Diagnosis of Cut, Incised and Split Wounds, by Abrasions Margin

V. Földes, R. Budvári

(Criminal Investigating Laboratory, Budapest)

The correct definition of cut, incised, and split wounds may sometimes present difficulties. Still, exact definition is often important this giving a clue for finding the injuring tool.

In differential diagnosis, the epithelial abrasions in the margin of the wound is the most important sign. The character of this abrasion depends on the injuring tool, the angle of its planes, its rough or smooth surface. These relationships have been studied in necropsy material and in experiments on cadavers. By gross and microscopic examination the mechanism of creating of the abrasion in the margin of the wound were established and the signs which may offer assistance in differential diagnosis have been discussed.

Spontaneous Rupture of the Aorta

L. Harsányi, Gy. Gorácz

(Dept. of Forensic Medicine, Medical Universtiy, Budapest)

50 lethal cases of spontaneous rupture of the aorta were examined. Cases of traumatic rupture served as controls. Further, the aortas of individuals died at about the same age from other diseases were used for comparative studies. The latter cases have not been selected on the basis of the gross appearance of the aorta. — The most frequent site of spontaneous rupture, the microscopic changes of the aortic wall, the pathogenetical and mechanical conditions giving rise to rupture have been discussed on the basis of an unparalleled large material.

Manometric Examinations on the Insufflation of Air into the Lungs of Newborn that Did Not Breathe

Gy. Farkas

(Dept. of Forensic Medicine, Medical University, Pécs)

It has been found that aeration of the lungs cannot be achieved unless a pressure equalling that present on active inspiration is applied. Resuscitation procedures are usually performed with a lower pressure, their eventual success must therefore be saught in a stimulation of the central nervous system (respiratory centre).

Alcohol-Barbiturate Synergism

J. Nagy

(Dept. of Forensic Medicine, Medical University, Debrecen)

The existence of a synergism between alcohol and barbiturates is well-known. The effect of Dorlotin (isoamyl-ethylbarbituric acid) is particularly increased by alcohol. In rat experiments doses of alcohol and Dorlotin ineffective by themselves induced narcosis on simultaneous administration. Further, comparatively harmless doses of the two drugs proved lethal when they had been ingested together. The latter fact is of a practical importance as, considering that in such cases death is preceded by long unconsciousness, neither alcohol determination nor the estimation of the narcotic drug will give an explanation for the lethal poisoning.

Changes of the Quotient Urine Alcohol : Blood Alcohol in Various Injuries and Intoxications

L. Buris

(Dept. of Forensic Medicine, Medical University, Debrecen)

In previous examinations the quotient urine alcohol : blood alcohol (U/S) has been studied after injuries and poisoning by narcotic compounds. — If the patient survived the injury or poisoning for a longer time, the quotient U/S increased, values ranging from 1.7 to 2.34 were found instead of the physiological values 1.1 to 1.4. In the present experiments, dogs poisoned with alcohol were subjected to cerebral injury resp. intoxication with Veronal. Following cerebral injury, the quotient did not change. In Veronal poisoning the quotient increased to 2.05 on the average.

The mucosa of the urinary bladder of dogs was found permeable to alcohol. *In vitro* the permeability of the urinary bladder to alcohol gradually ceased.

The claim of WEINING and SCHWERD that the human bladder is less permeable to alcohol han ¦that of the dog has not been confirmed by the present observations.

A kiadásért felel az Akadémiai Kiadó igazgatója

Műszaki felelős: Farkas Sándor

A kézirat nyomdába érkezett: 1959. III. 11. — Terjedelem: 5,75 (A/5) ív

Akadémiai Nyomda, V., Gerlóczy utca 2. — 48416/59 — Felelős vezető: Bernát György

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