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On supportive therapy for osteo- and chondropathy

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1. Introduction

According to current knowledge, the therapy of osteopathy and chondropathy has to be categorized as being somewhat problematic. For this reason, each new therapeutic method should be checked carefully regarding its possible applications. This article concerns itself with Gerontamin® *) as therapeutic agent and reports on initial experiences with this preparation.

1.1 Biochemical basis

Bone tissue consists of an organic and an inorganic matrix and undergoes constant replacement during its lifetime. The organic bone matrix contains 93% collagen, 5% protein, 1% proteoglycanes (acid mucopolysaccharides) and 1% citrate. Non-mineralized bone substance is designated as osteoid. The osteoid layer, formed on a daily basis from osteoblasts and young osteocytes, is approximately 1µm thick. In the course of the mineralization of bone, hexagonal hydroxylapatite crystals are formed within the nucleation centers. The composition of cartilage varies strongly according to origin and function.

Collagenous connective tissue consists essentially of the scleroprotein collagen [1-4] which is characterized by its high proportion of glycine and by the unusual amino acids hydroxyproline and hydroxylysine. The sequence of amino acids in collagen is remarkably regular. As shown in figure 1, every third residue is glycine; in addition, the sequence glycine-proline-hydroxyproline is frequently repeated.

13
-Gly-Pro-Met-Gly-Pro-Ser-Gly-Pro-Arg-
22
-Gly-Leu-Hyp-Gly-Pro-Hyp-Gly-Ala-Hyp-
31
-Gly-Pro-Gln-Gly-Phe-Gln-Gly-Pro-Hyp-

Fig. 1: Amino acid sequence of a portion of the α_1-chain of collagen. According to [4].

The biosynthesis of collagen takes place initially intracellularly in several steps. The characteristic amino acids hydroxyproline and hydroxylysine are first hydroxylated within the protein group. Thus, initially, a hydroxyproline-free protein (protocollagen) is formed. The hydroxylation of proline takes place via protocollagen hydroxylase; this also requires iron(II) ions, α-ketoglutarate and ascorbic acid in addition to O_2.

The primary products of collagen biosynthesis are the α-chains of which 2 types are known, α_1 and α_2, each of which has a slightly different composition. Each of these chains has a molecular weight of approximately 100,000, two α_1 chains and one α_2 chain configured in a form of a rectangular superhelix and with a pathway of 2.9 nm. One portion of the hydroxyl groups of the hydroxylysine is now linked via a ß-glycoside bond with a galactose residue onto which an α-glycosidic-bound glucose residue is transferred (fig. 2).

*) Manufacturer: Heilit Arzneimittel GmbH, 2057 Reinbek

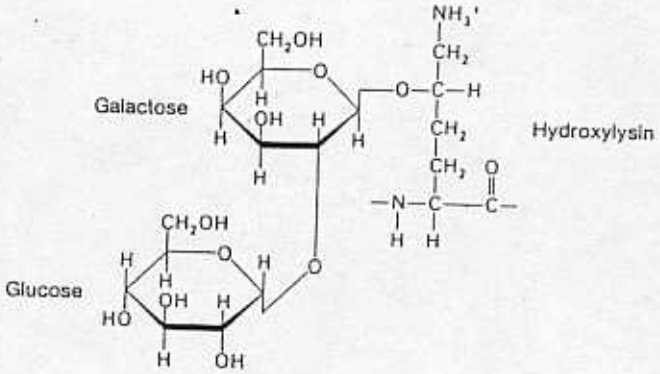

Fig. 2: Coupling of the disaccharide unit to the hydroxyl group of a hydroxylysine residue

The end product of intracellular collagen biosynthesis is a collagen that is soluble in neutral salt, a thin rod-like molecule of 280 nm in length and 1.5 nm thick: procollagen. This is then excreted into the extracellular space whereby an approximately 70-amino acid-long peptide (register peptide) is split off the N-terminal by procollagen peptidase. The monomeric collagen (tropocollagen) thus created now forms fibrils characterized by a quadruple configuration of the tropocollagen molecule. In this way, long microfibrils with a periodicity of approximately 70 nm are formed from the relatively short tropocollagen molecules.

These fibrils originating from a process of parallel aggregation are stabilized by the formation of covalent bonds. Thereby, lysyl- and hydroxylysyl residues are deaminated by copper-dependent lysyloxidase. The aldehydes thus formed form a cross-linking matrix with other aldehydes or with the ε-amino groups of other lysyl or hydroxylysyl residues (fig. 3).

During this process, collagen microfibrils are formed which can be regarded as scleroproteins and which are insoluble in neutral salt solutions.

In most connective tissue, elastin [5, 6] is associated with collagen and mucopolysaccharides. It is the principal component of elastic fiber. Similar to collagen, approximately one third consists of glycine residues. Proline is also present in considerable amounts whereby hydroxyproline is almost completely absent. Hydroxylysine is not at all present.

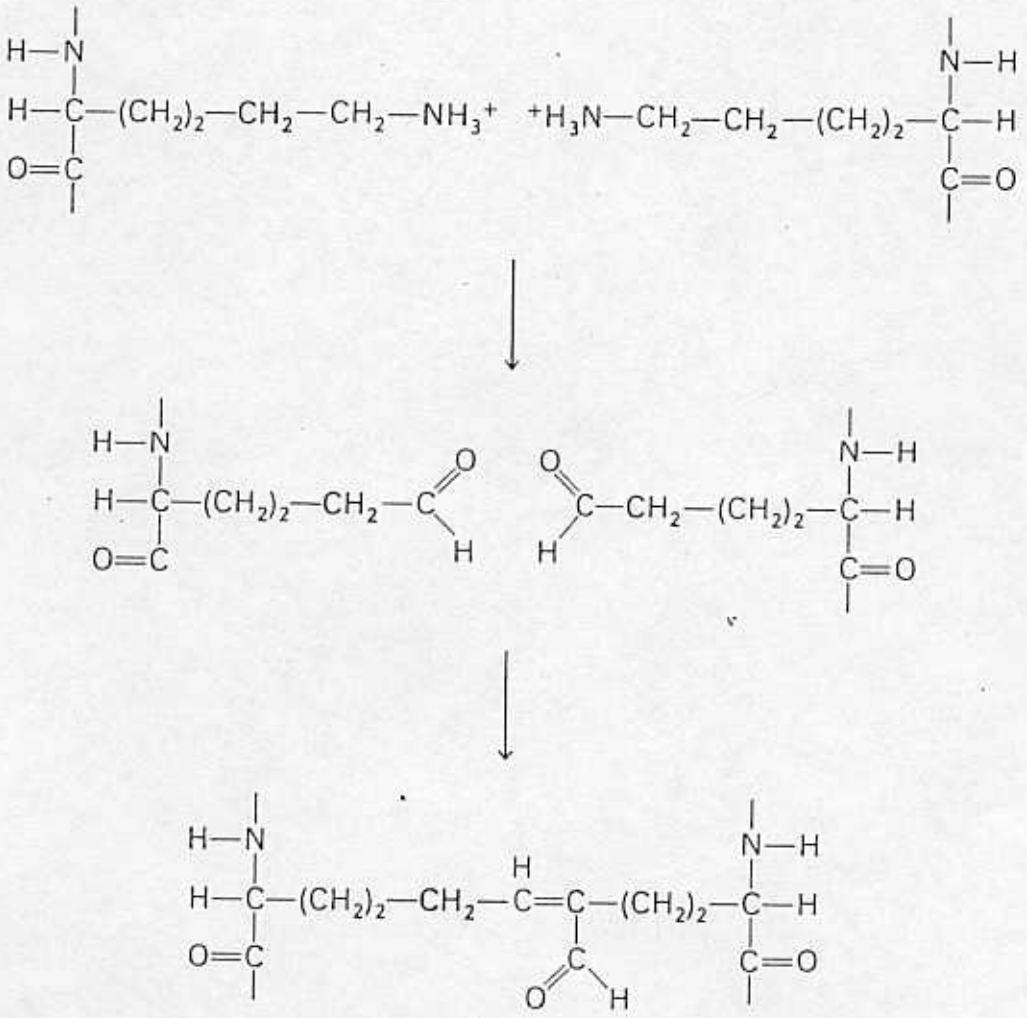

Fig. 3: (I) : Lysine residues; (II): Aldehyde derivatives; (III): Aldol bridges

Elastin's color and, partially, its mechanical properties are the result of its possessing two unusual amino acids, desmosine (fig. 4) and isodesmosine. Another type of cross-linking originating from lysine and which is also present in collagen is the lysinonorleucine cross-linking.

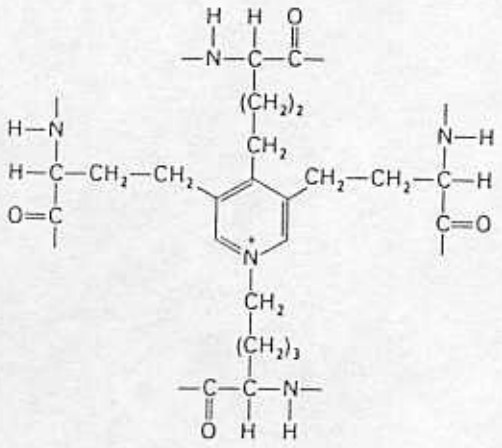

Fig. 4: Desmosine

The acid mucopolysaccharides (glycosoaminoglycanes) are polyanionic linear polymers comprising alternate acetylated or sulfated amino sugars and uronic acid or galactose. Sulfate ester groups can also be included. The mucopolysaccharides differ only in the monosaccharides involved as well as in their binding character and sulfate content. They are formed in the endoplasmic reticulum and occur in tissue mostly in their non-native form and covalently bonded with specific proteins in the form of proteoglycanes.

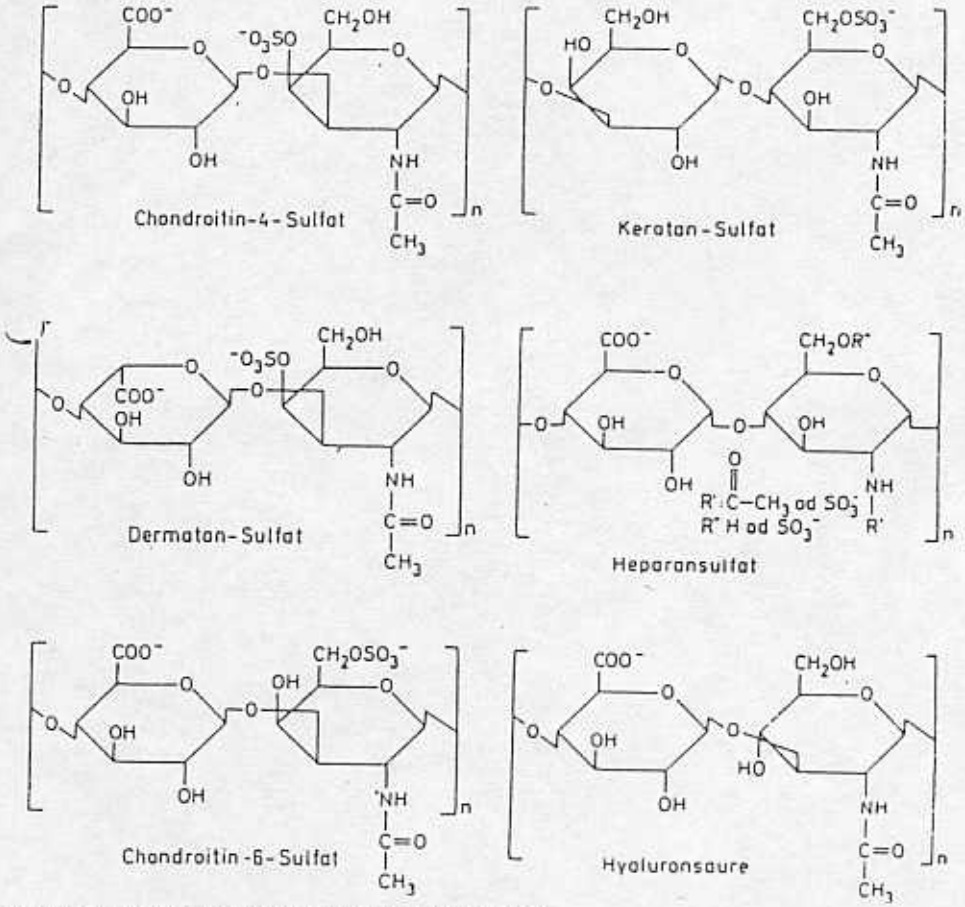

Fig. 5: Structural formulae of the glycosoaminoglycanes

In principle, proteoglycanes have a similar structure to glycoproteins, the difference being in the prosthetic groups involved. More than two monosaccharide types in irregular sequence are usually involved in the glycoprotein structure.

1.2. Pathophysiological basis

The assessment of pathogenic alterations must be considered with respect to the background of age-dependent physiology [7]. The various types of connective tissue progress through differing maturation processes whilst for example ligaments and tendons are rapidly differentiated and cornea and heart valves retain the condition they had at birth.

The ageing procedure is characterized by an increase in the number of hydrogen bridges and ester bonds between the tropocollagen molecules. In the senium period for example, mucopolysaccharides are formed in ligament tissue which then loses its resistance to tear. The adhesive substance between individual fibers becomes thinner, they become more densely packed and the water content decreases. In mixed tissue, the relation between reticular and collagenous fibers also alters. The glycosamineglycane pattern alters as a function of cell differentiation and the keratin sulfate content of cartilage increases from the exterior to the interior.

At the beginning of life, cartilage contains 90% chondroitin sulfate; in the course of life, this is gradually replaced by keratin sulfate. In the case of certain illnesses, this substitution can be accelerated by up to ten years [8]. The quotient hexosamine / sulfate e.g. the degree of sulfation of chondroitin sulfate decreases. On the other hand, the keratin sulfate content of the knee joint decreases with increasing age whereby the proportion of chondroitin sulfate does not alter. In cases of arthrosis of the knee joint, the amount of glycosaminoglycane peptides decreases whereby keratin sulfate and chondroitin sulfate are affected to the same extent. Overall, an immature cartilage is formed, a fact that represents the essential basis of therapy with Gerontamin®.
In this immature cartilage, identical in many cases to the "pseudo cartilage" referred to by clinicians, elastic property is lost; it becomes asbestos-like and hence harder, loses its metachromatism and becomes thinner. Its nutrition becomes deficient as this is dependent on the molecular condition of the glycosaminoglycane proteides. The collagen fibers compete with the chondroitin sulfate proteides for calcium with the result that their calcium binding capacity decreases. The consequence is a clearly identifiable subchondral bone formation (subchondral osteoporosis).
This subchondral osteoporosis is the clinical substrate of degenerative disease of the skeletal apparatus. It can be identified by X-ray as an early symptom of arthrosis and several authors are of the opinion that its cause is deficient callus formation subsequent to microfracture.
This calcified callus is said to occur through loss of the shock-absorbing properties of the altered cartilage. Pain that constantly accompanies such degenerative alterations is caused by non-shock absorbed shock transfer in subchondral bone. In particularly painful periostic autolytic bradykinines, prostaglandins and other pain-causing substances are released; on the one hand this gives rise to intensive pain, and on the other it induces further self-destructive processes in the disintegrating cartilage [5, 10].
Certain metabolic diseases, especially diabetes, particularly favor the appearance of spondylosis, possibly brought about by insulin-dependent deficiency in glycosylamine glycane synthesis. In other metabolic diseases, such degeneration is promoted by disease-specific degenerative products. For example, in the case of alcaptonuria, homogentinic acid is deposited in cartilage and in the nucleus. Homgentinic acid inhibits hyaluronidase and cross-links the basic substance. In this way, calcium salts are precipitated and substance transport is prevented. In the case of gout, similar mechanisms lead to the precipitation of urates at typical sites. Chondrocalcinosis is caused by the precipitation of calcium pyrophosphate in cartilage, meniscus and invertebral disks, and ectopic calcification is caused by the precipitation of calcium salts. LEHNINGER [11] recently published an interesting theory on calcification; the hypothesis was that the precipitation of calcium salts always takes place in two stages:

$Ca^{1+} + HPO_4^{2-} \rightarrow Ca_3(PO_4)_2 + H^+$ (amorph) (I)
$Ca_3(PO_4)_2 + H_2O \rightarrow [Ca_3(PO_4)_2]_3\ Ca(OH)_2 + H^+$ (II)

In such a case, amorphous calcium phosphate is the obligatory precursor to hydroxylapatite formation. Whilst amorphous phosphate is soluble and can be regarded as a physiological transport medium, hydroxylapatite is completely insoluble. Amorphous calcium phosphate is transported in the form of incrusted mitochondria; uptake in mitochondria takes place with the uptake of energy (ATP cycle). The decoupling of inhibitors is decisive in the formation of hydroxylapatite (stage II) the most important of the inhibitors being phosphocitric acid. This would explain the relatively high concentration of citric acid in bone.

The occurrence of invertebral disk degeneration is closely associated with the basic tension placed upon the fibrous ring by the water-rich pulp of the invertebral disk. During the ageing process, the water content and hence the turgor of the pulp decreases. The physiological mixture of the glycosaminoglycanes, normally consisting of equal proportions of chondroitin-6-sulfate and keratin sulfate, is characterized by an increasing proportion of dermatan sulfate. The same proportions are found in prolapsed mucous cores [7, 12]; in such cases, the viscosity is lower than would be expected for the age involved. The fibrous ring then ruptures due to mechanical stress.

In cases of degeneration of ligament tissue, a disorientation of the fibrils [7] can be established using polarization techniques. Under the electron microscope, two fibril populations can be recognized and seen to have a shortened periodicity. Similar changes can be established in cases of damaged meniscus.

As one of the important indications of the preparation Gerontamin® is the healing of bone chondroplasty (see below), the molecular pathological processes that take place during wound healing will be briefly mentioned. It would appear that glycosamine glycanes are important in wound healing. Cartilage powder (especially from young individuals), collagen powder and chondreotin sulfate promote wound healing when placed on the wound [7].

Table 1 shows the percentage composition of glycosaminoglycanes of a mature Achilles tendon of the rabbit subsequent to rupture.

Table 1: Glycosaminoglycanes of a mature Achilles tendon of the rabbit prior to, four days and four months subsequent to rupture.
I. Hyaluronic acid; II. Chondroitin-4-sulfate; III. Chondroitin-6-sulfate; IV. Dermatan sulfate. According to HARTMANN and DEICHER [7]

	Prior to	4 days	4 months
I	16	56	20
II	7	11	9
II	9	8	8
IV	60	12	54

The table shows that practically only hyaluronic acid and keratin sulfate are involved in the changes that take place. Glycosaminoglycanes and galactosaminoglycanes are reduced during the formation of scar tissue.

Specific information with respect to the pathobiochemistry of congenital and acquired connective tissue disease can be obtained from the literature [7,8,13].

2. The preparation and its effect

Gerontamin® is available in both capsule and powder form for oral therapy. The capsules contain 0.69 mg vitamin A acetate (corresponding to 2000 I.U. vitamin A), 10.00 mg L-cystine and 579.78 mg gelatin. One sachet of powder contains 8.2 mg vitamin A acetate (corresponding to 24000 I.U. vitamin A), 120.00 mg L-cystine and 7011.74 mg gelatin.

2.1. The active ingredients

2.1.1. Vitamin A

The essential effect of vitamin A is based on its properties with respect to membrane activation [14]. Whilst low concentrations are required for the stability of biological membranes, overdosing results in the release of lysomal enzymes with all their biological consequences.

Deficiency of vitamin A accelerates the degradation of mucopolysaccharides. Bone growth is thus considerably affected [16].

In addition, vitamin A has considerable effect on the function of cartilage cells and is thus important for skeletal growth. Deficiency of vitamin A damages chondroblasts and brings enchondral bone growth to a stop. It is assumed that the normal equilibrium between formation and resorption

becomes imbalanced due to the changes brought about in the intermediate metabolism of supporting substances. In cases of Scheuermann's disease, a reduced level of vitamin A in blood is frequently reported. Changes in bone growth can bring about interference in the maturation of fiber cartilage with subsequent necrosis formation. Such changes can lead to penetration of vertebral tissue into the vertebral body spongiosa; this in turn can lead to necrosis of the cover plates and crests.

2.1.2. Cystine

The sulfur-containing amino acid cystine is not in fact essential; however, it plays an important part in sulfur metabolism. For this reason, Gerontamin® was supplemented with cystine due to the fact that the carrier of the therapeutic agent of the preparation, gelatin, is known to be deficient in this particular amino acid. The specially pure and partially hydrolyzed gelatin used in the preparation of Gerontamin® is practically free of cystine (see below).
The therapeutic effect of cystine in Gerontamin® is based on the fact that when it is degraded by a stepwise oxidation of the thiol groups, cysteic acid is formed which is then converted into taurine and sulfopyruvate. The sulfate group of sulfopyruvate, once it has been activated by ATP, is then available for the biosynthesis of biologically important substances containing sulfate ester groups (sulfatides, mucopolysaccharides), which in part play an important role in the metabolism of support substances. In addition, cystine and cysteine are of general importance.

2.1.3 Gelatin

Gelatin is one of the most important substances required for the biosynthesis of collagen. It is extracted from collagen by boiling with dilute acid. The gelatin used in the manufacture of Gerontamin® contains 5.1% hydroxyproline and 2.6% hydroxylysine. Due to the special purification process used, the product is cystine-free. When gelatin is ingested or administered intravenously, hydroxyproline and hydroxyproline-containing oligopeptides can be detected in substantial quantities in urine [14, 18]. The occurrence of oligopeptides is probably due to a deficiency of proline pepsidases in the lower duodenum. It may be assumed that the administration of gelatin over a longer period of time gives rise to the formation of a hydroxyproline pool within the organism from which amino acids can be taken as required. This should also apply to hydroxylysine although the question as to when and where hydroxylation takes place still has to be clarified [17].

2.2 Indications and effect
2.2.1 Indications

The indications for the use of Gerontamin® are as follows: Supporting therapy in degenerative disease of the vertebral column and the small intervertebral joints (spondyl arthrosis, spondylosis, osteochondrosis; Scheuermann's disease, joint arthrosis, chondropathy patellae, chondromalacia; post-traumatic cartilage damage in youth; osteoporosis, in particular affecting the vertebral column, involution osteoporosis and cortisone osteoporosis). In addition, the preparation accelerates the healing of orthopedic transplants.
Experience gained in using the preparation repeatedly shows an improvement in the general condition, a loosening of the degree of movement of the vertebral column, freedom from pain and relaxation of the musculature. Occasional reports have also been received concerning a reduction of the susceptibility to lumbago and on an increase in elasticity of the connective tissue of the vertebral column segments.
Positive reactions have also been received with respect to diseases of the young, particularly in cases of the larvated form of Scheuermann's disease. In most cases, freedom from symptoms was achieved. According to X-ray analysis, the disease had become stationary and in some exceptional cases less progressive. As is shown by the treatment of chondropathy patellae and osteochondritis dissecans during the initial stage of the disease, cartilage that is still capable of reaction and participating in metabolism is a precondition for therapeutic success. In the case of osteochondritis dissecans, relapse could be prevented in cases where the disease could not yet be established by X-ray. However, in cases of definite X-ray diagnosis of disease, a stage of degeneration may be achieved whereby supportive therapy with Gerontamin® may not be fruitful.
This indicates that in the case of cartilage and bone tissue of young people, the therapeutic effect is established at an earlier stage and can be regarded as being more intensive and longer lasting. In the

case of older patients with metabolically stressed tissue, less success can be expected. An additional factor is that even healthy cartilage-bone-tissue belongs to the type that is less active metabolically.

Sometimes, particularly in cases involving the intervertebral joints, so-called pseudo-cartilage can be detected by X-ray. This type of cartilage is referred to as pseudo-cartilage because regeneration of already degenerated cartilage is not possible. Cartilage-similar substance can only be formed subsequent to the administration of a suitable substrate. In view of these considerations, the group of secondary cartilage degeneration subsequent to infection is just as interesting for treatment with Gerontamin® as the healing process of bone cartilage chondropathy in cases of osteochondritis dissecans.

It must be continuously emphasized, however, that treatment with Gerontamin® is a supportive therapy only and that the healing rate can decrease if massive degenerative changes can be established by X-ray or if older tissue with respect to metabolic activity is involved.

From the above, the following can be concluded: On the one hand, Gerontamin® would appear to stimulate protein metabolism whilst contributing on the other hand to regeneration of cartilage tissue and connective tissue. The effect of the preparation is to be understood as substitution therapy.

3. Clinical experiences [18]

Gerontamin® has up to now been clinically tested at three locations.

3.1. Report 1

During the period 1971 - 1973, a total of 120 orthopedic cases were treated with Gerontamin®. The age of the patients was 13 to 70 years. Corresponding to this rather large age group, the patients were split into groups comprising young people up to the age of 35 and a group older than 36. This resulted in the creation of "young" and "old" tissue. Further allocation was carried out on a schematic basis.

The clinical effect of Gerontamin® on various joints (vertebral joints, knee and ankle joints etc.), Scheuermann's disease and degenerative vertebral column conditions diagnosed by X-ray at the beginning and at the end of medication as well as during subsequent investigation carried out over a period of three years subsequent to successful treatment. The clinical evaluations as well as the subjective information provided by patients were assessed whereby information provided by psychologically affected and neurotic patients was not taken into account.

The preparation was administered over a period of 1, 2, 3 or 6 months at a dose 7.0 g per day. In 70 cases, the preparation was administered for one month in 8 cases for two months, in 38 cases for three months and in 4 cases for six months.

Most patients found Gerontamin® excellently compatible even in cases of hyperacidity and anacidity, no side-effects being registered. Even patients with gall bladder conditions and those having recovered from hepatitis found Gerontamin® compatible. On the other hand, hyperacid patients occasionally complained of heartburn, emptiness in the stomach and reflux; however, treatment did not have to be interrupted in any of these cases.

In all cases of larvate Scheuermann's disease, freedom from symptoms was achieved. In the case of more advanced form of the disease as detected by X-ray, freedom from symptoms was partially achieved, the X-ray diagnosis remaining essentially stationary. In some cases, the disease remained progressive in spite of medication but in attenuated from.

Chondropathy of the patella responded to treatment only in the early and medium stages of the disease; later forms showing irreversible damage to cartilage remained uninfluenced. Of the two early stages investigated, one month was all that was required to obtain freedom from symptoms; within the subsequent three-year period, no relapses were recorded.

Progress of osteochondritis dissecans was only able to be influenced during the initial phase of the disease and patients became free of symptoms. Relapse was not reported during the subsequent observational period. Also, no changes were noted on subsequent X-ray pictures. In those cases were

the focus of the osteochondritis had been localized clearly by X-ray, the impression was obtained that long-term treatment may well have achieved higher success. Success was not expected during the demarcation stage; in such cases, no satidfactory results were obtained.

No real success was obtained in cases of post-traumatic cartilage damage of the joints within one year in spite of treatment. Minor post-traumatic cartilage damage in young people could not be included in the investigation.

In the case of group B (old tissue), it can be said that the success of treatment decreased with increasing age, finally reaching a stage where the condition could no longer be influenced by the administration of Gerontamin®. The severity of the disease was also of course an essential factor in these cases.

On the basis of the results of the investigation obtained over a period of three years, it is quite clear that the successful treatment of joint damage is dependent on the presence of cartilage capable of reacting and active with respect to metabolism and that the effect of the preparation - assumed to be established - is in direct correlation with the regenerative power of the joint cartilage. For this reason, it is also understandable that young and youthful cartilage and bone tissue undergoes successful treatment, both subjectively and objectively, and that the effect occurs considerably earlier, more intensively and is of longer duration than is the case with older patients whose tissue is no longer so metabolically active.

With respect to the duration of treatment, it can be said that a period of three months on average is suitable for most of the diseases of group A; only in the case of Scheuermann's disease should the period of treatment (3 months - 6 months interval - 3 months) have a more favorable influence on the disease. In group B, it would have been favorable to administer Gerontamin® for longer than one month whereby the dosage could have been reduced after the first month.

In summary, based on the experience of a three-year study, it can be said that Gerontamin® can be successfully employed for the treatment of various orthopedic diseases without giving rise to side-effects - apart from a few rare occurrences in already damaged stomachs.

3.2 Report II

The preparation was employed during the period 1976 - 1977 in an orthopedic university polyclinic on 17 patients with the following conditions: degenerative changes in the vertebral column and peripheral joints, primarily knee joints, both in the sense of knee arthrosis and in the sense of a chrondopathy of the patella (especially in younger patients).

The age of the patients was between 16 and 69 years; they suffered from chronic symptoms, especially subsequent to longer periods of stress. The period of duration of symptoms was as a rule more than one half to one year. The preparation was administered on an average over three months. The dosage was either one sachet daily or alternatively eight capsules. With the exception of one patient, administration was not interrupted.

Eight patients experienced satisfactory improvement of their symptoms, one patient reported on a slight improvement and in eight patient there was no improvement.

Compatibility was assessed differently. In eight cases, stomach or digestive symptoms were indicated. The remainder of the patients indicated no such incompatibility. In this connection, the following observation should be noted: With one exception, the stomach and digestive disturbances were indicated by those patients who experienced good to very good improvement in pain whilst patients who experienced no improvement also had no such incompatibility symptoms. It is quite possible that in the group showing good treatment success, such stomach symptoms have to be accepted whilst patients with less treatment success possibly took the preparation at irregular intervals or in lower doses than prescribed, hence suffering no incompatibility reactions but also no success with respect to treatment.

3.3. Report III

Gerontamin® was employed for the treatment of 56 patients of which 43 were female, and 13 male. The age of the patients was between 50 and 75 years. 12 patients interrupted treatment and 3 did not appear for subsequent examination.

Cases of osteochondrosis, spondylosis and arthrosis were taken on for treatment, most of these at an advanced stage and one of which was an advancing osteoporosis. In 30 cases, hair or nail changes were observed.

Very good success was achieved in 10 cases; 5 patients indicated complete freedom from pain and 5 improvement in their general condition. Objectively, there was a loosening of the degree of movement of the vertebral column along with a relaxation of the musculature. 18 patients indicated noticeable improvement. In the case of 12 patients, the general situation improved considerably and in 6 patients pain had receded substantially. In this group, the majority of patients experienced a substantial relaxation of the musculature whereas the degree of movement only improved in individual cases. The reduced level of pain was the principal factor involved in most cases; in discontinuation of the preparation pain returned in some cases.

In 13 cases, no changes were indicated. 8 patients indicated an improvement in hair and nail growth, 22 showed no change.

The preparation was administered for 5-6 months on average (initially 7.0 g per day for 2 to 3 weeks followed by 5.0g).

Subsequent examination produced the following results: In 25% of the patients treatment was designated as being very good, in 45% as substantially improved whereas 30% indicated no improvement.

Summary
Gerontamin® contains vitamin A, L-cystine and gelatin as active ingredients in practically equal proportions. The preparation is used for the supportive therapy of degenerative disease of the vertebral column and the smaller intervertebral joints; Scheuermann's disease, arthrosis of the joints; chondropathy of the patella; chondromalacy. In addition, it can be used in cases of post-traumatic cartilage damage in youth as well as in cases of osteoporosis. Gerontamin® was used in three clinical studies involving almost 200 patients with the most various of diseases. In general, a relaxation of the musculature, lessening of pain, improvement of the degree of movement of the vertebral column and improvement of the general condition were reported. Occasional reports have been given concerning improvement in connective tissue elasticity and a decrease in the susceptibility to lumbago.

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