

and sixteen months have now elapsed from that date. In that time he has gained over 26 lb. (11.8 kg.) in weight. There remains only faint staining of the skin over his elbows and a minute trace of albumin in the urine, the centrifuged deposit containing no abnormality. His blood pressure and E.S.R. are normal. He has completed his schooling, and is an apprentice in a sheet-metal factory.

Discussion

Although the history and clinical findings were characteristic of polyarteritis nodosa, we were fortunate in obtaining early histological proof of the diagnosis. The absence of polymorphonuclear leucocytosis and eosinophilia does not confound the diagnosis, for Miller and Daley (1946) state that the former finding occurs in 70% of cases, whilst eosinophilia is relatively unusual, being found in approximately 20%. Our patient gave no antecedent history of a specific infection or of upper respiratory tract infection, and he had taken no drugs before his illness.

It cannot be stated categorically that he would not have recovered spontaneously, though the clinical course certainly suggested otherwise. There is no doubt that improvement dated from the beginning of treatment with A.C.T.H. and, furthermore, that from that time a prolonged remission was established. The plan of treatment differed from that set out by Mundy *et al.* (1951) in that a prolonged consecutive course of A.C.T.H. was given, and was continued until all clinical and laboratory signs of activity had subsided. Whether the patient can be regarded as cured can be determined only by prolonged surveillance.

Summary

A case of polyarteritis nodosa in an acute phase is presented, with clinical and pathological findings. Treatment was provided with intramuscular A.C.T.H., which was continued until no clinical or laboratory evidence of activity was forthcoming.

Complete remission of the disease process for over one year to date has been achieved.

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Rabies is still an acute problem in many parts of the world where dogs are often in contact with wild animals. The World Health Organization's Expert Committee on Rabies has been meeting in Rome this week to examine new developments resulting from large-scale experiments in rabies control sponsored by W.H.O. in Spain, Greece, Yugoslavia, Mexico, and other countries. In this second session in three years the Committee has discussed various improvements in types of vaccines for human and veterinary use. The success of canine vaccination in many countries, including the United States, has been reviewed, and the Committee has received reports on systematic treatment with hyperimmune serum in Iran among people bitten by rabid wolves, and on the local treatment of wounds in laboratory animals in Spain. Another task of the Committee was the final approval of the text of the W.H.O. *Manual of Laboratory Techniques in Rabies*, which is designed to standardize laboratory procedures and facilitate comparison of international experiments. Training courses and meetings are organized by W.H.O. to spread information on new and effective techniques of rabies control throughout the many countries which, unlike England, Switzerland, and the Scandinavian countries, have been unable to achieve complete control of the disease.

COMPOSITION OF ARTICULAR CARTILAGE IN OSTEOARTHRITIS CHANGES IN COLLAGEN/CHONDROITIN- SULPHATE RATIO

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The bluish-white hyaline cartilage of healthy articular surfaces is a smooth, glistening, and resilient tissue, and it is here that the earliest morphological changes characterizing osteoarthritis or degenerative joint disease appear. Opacity and yellow discoloration accompanied by progressive loss of elasticity are evidence of senescent change preceding the appearance in the surface layer of small blisters, grooves, and pits. Later, as larger circumscribed erosions approach the underlying bone, the articular surface assumes a velvety appearance and spongy texture resulting from loss of intercellular substance and exposure of collagen fibres. Histologically, the affected cartilage is cleft along its fibrillary planes, and, since the superficial fibres are tangentially arranged, the earliest lesion is horizontal flaking of the surface cartilage. Ultimately, as extension along the path of radially disposed collagen bundles occurs, splitting and the concomitant loss of tissue result in exposure of subchondral bone. Fibrillation, as this process is known, is the hall-mark of osteoarthritis.

These changes occur first and foremost in weight-bearing joints. In the knee, fibrillation of articular cartilage occurs principally in those areas in which weight-bearing is concentrated, and which are most subjected to shearing stress (patella, exposed portions of the tibial condyles, patellar surface of the femur, and the anterior and middle thirds of the medial femoral condyle) (Bennett *et al.*, 1942).

Little work has been devoted to chemical aspects of fibrillation. Preliminary data (Matthews, 1952), dealing with the proportions of the two main organic components of healthy articular cartilage, indicated the importance of mechanical function in determining the ratio of collagen to chondroitin sulphate. Using similar chemical methods, we have investigated this ratio in fibrillar articular cartilage compared with that of healthy cartilage within the same joint.

Materials and Methods

The material was taken at necropsy. A knee-joint was opened, and, after flexing the joint fully, the articular surface of the lower end of the femur was inspected for fibrillar lesions. Knee-joints showing frank degenerative change more than fibrillation were not used, since they yielded insufficient material for analysis.

The areas selected for this investigation, therefore, were moderately advanced circumscribed lesions, about 2-3 cm. in diameter, showing fibrillation with loss of superficial cartilage, and affecting the medial condyle and the patellar surface of the femur, or the medial condyle alone. The whole of the fibrillar material constituting the lesion was excised with a sharp scalpel, care being taken to exclude the healthy adjacent and underlying articular cartilage. For control material, a piece of healthy cartilage of similar area and thickness was pared from a corresponding site on the

lateral femoral condyle. When fibrillar cartilage was taken from the patellar surface of the femur, healthy cartilage was also removed from an adjacent area. Cartilage from the weight-bearing areas of the medial and lateral condyles and from the patellar surface of the femur of healthy adult knee-joints without fibrillation served as a further control. Cartilage samples obtained in this way were finely divided with a scalpel, dehydrated in several changes of acetone, and finally dried over concentrated sulphuric acid *in vacuo* to constant weight. Determinations of collagen and chondroitin sulphate on aliquots were carried out as previously described (Matthews, 1952).

Results

The accompanying table gives results obtained from seven knee-joints showing twelve comparisons between fibrillar and healthy cartilage. Five joints showed lesions of both medial condyle and patellar surface, while in two the medial

Collagen and Chondroitin Sulphate Content of Fibrillar and Healthy Articular Cartilage in the Knee (% of Dry Weight)

Case	Age	Hydroxy-proline as Collagen	Hexosamine as Chondroitin Sulphate	Collagen/Chondroitin-sulphate Ratio	Mean of Ratios	Hydroxy-proline as Collagen	Hexosamine as Chondroitin Sulphate	Collagen/Chondroitin-sulphate Ratio	Mean of Ratios	
Fibrillar Cartilage: Weight-bearing Surface of Medial Femoral Condyle						Healthy Cartilage: Weight-bearing Surface of Lateral Femoral Condyle				
1	42	53.3	13.2	4.0	} 3.67 s.d. 1.18	45.0	21.6	2.1	} 2.09 s.d. 0.33	
2	49	62.3	14.8	4.2		52.5	20.8	2.5		
3	64	56.3	20.0	2.8		50.3	26.0	1.9		
4	68	51.8	20.0	2.6		45.0	23.2	1.9		
5	68	62.3	10.4	6.0		54.0	22.0	2.5		
6	78	52.5	16.8	3.1		45.8	21.6	2.1		
7	81	47.3	15.6	3.0		44.3	27.6	1.6		
5 control cases without fibrillation aged 45-75		Weight-bearing surface: medial femoral condyle			1.94 s.d. 0.09	Weight-bearing surface: lateral femoral condyle			2.10 s.d. 0.07	
Fibrillar Cartilage: Patellar Surface of Femur						Adjacent Healthy Cartilage: Patellar Surface of Femur				
1	42	60.0	15.7	3.8	} 5.16 s.d. 2.54	48.0	20.4	2.4	} 2.34 s.d. 0.20	
3	64	57.8	18.4	3.1		54.8	22.0	2.5		
4	68	50.3	8.4	6.0		53.4	21.5	2.5		
5	68	60.8	9.2	6.6		53.2	23.0	2.3		
6	78	60.8	9.6	6.3		50.2	25.0	2.0		
5 control cases without fibrillation aged 45-75		Patellar surface of femur				2.12 s.d. 0.07				

condyle only was affected. Additional results obtained from five control subjects whose ages ranged from 45 to 75 years, and in whom there was no evidence of fibrillation within the knee, are included.

It is evident that in fibrillar lesions of articular cartilage in the knee the collagen/chondroitin-sulphate ratio is greater than in healthy cartilage from the same joint; the ratios obtained for the latter agree well with those found for comparable sites in healthy joints.

The water content of the samples analysed was not determined. This value was readily obtained for smooth, healthy articular cartilage; but in fibrillar material, where a variable amount of extraneous water is held in the interstices, the true state of hydration is difficult to determine.

Discussion

The present-day morphological concept of fibrillation gains support from chemical analysis: the increased collagen/chondroitin-sulphate ratios found (as compared with healthy cartilage) reflect chemically the different rates of loss of these substances in cartilage undergoing fibrillation. As continued loss of cartilage tissue occurs, the more durable collagen fibres, though architecturally deranged, are lost at a slower rate than matrix substance. Although to the naked eye the areas of fibrillar cartilage analysed were of approxi-

mately similar severity, the ratios showed marked variation. Histological evidence of variation in the degree of fibrillation could not be obtained because the entire material removed was needed for analysis. It is conceivable, however, that, as the fibrillation process evolves, the extent to which intercollagenous matrix is lost is variable from lesion to lesion.

Fibrillar lesions of cartilage are an expression of injury (Collins, 1949). Though it cannot be stated that fibrillation is initiated by mechanical factors alone, it is clear that once a breach has occurred in a smooth articular surface they then become potent pathogenic stimuli. The results reported therefore throw no light on the earliest chemical changes which must occur in articular cartilage before even incipient evidence of fibrillation appears.

While the nature of this early change remains unknown, it is reasonable to suggest that it primarily involves chondroitin sulphate. Thus Benninghoff (1925a, 1925b) concluded from histological studies that depletion of matrix (containing chondroitin sulphate) renders the superficial cartilage and its bared fibrils vulnerable to pressure, permitting the development of both circumscribed defects and generalized flattening. In normal cartilage Hirsch (1944) has emphasized the importance of chondroitin sulphate in maintaining elasticity; and Matthews (1952) has shown that in normal weight-bearing or mechanically stressed cartilage the proportion of chondroitin sulphate is increased. Conversely, in patellar articular cartilage undergoing fibrillation, loss of resilience is accompanied by a diminution in mucopolysaccharide content (Hirsch, 1944). Once initiated, the evolution of fibrillation is the result of a vicious circle in which loss of chondroitin sulphate leads to decreased resilience, which in turn facilitates the mechanical perpetuation of the process.

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Medical Memoranda

Diabetic Coma Associated with Lipaemia and Complicated by Uraemia

Although many cases of lipaemia associated with diabetic coma have been reported, the following case is of interest because of the marked degree of lipaemia attained, with the manifestation of lipaemia retinitis, and also because of the unusual feature of temporary kidney dysfunction.

CASE REPORT

A married woman aged 22 was admitted to hospital on August 9, 1951, deeply unconscious, with a history that, since an apparently normal pregnancy ten months previously, she had been complaining of weakness, and for the past three weeks of loss of weight and polyuria. She had been unconscious for about ten hours before admission.

On examination the patient could not be roused by painful stimuli. Her temperature was subnormal. A pustular rash was present over the extensor surfaces of the knees and elbows, consisting of raised yellowish white nodules, 2 to 3 mm. in diameter, with an erythematous periphery. Her blood pressure was 70/50. The pulse was 102 regular, and of fair volume. The pupils were small and reacted equally to light; corneal reflexes were absent. All tendon reflexes were absent. The extremities were flaccid. Fundi: the disks were normal; all vessels presented a waxy-white