which one may well adopt is this: Could I make that assertion before a board of medical examiners if my qualifying diploma depended upon it? Viewed from this standpoint, I am afraid that I should have been forced to plough a medical witness occasionally if I had been one of the examiners. When expressing an opinion in the witness-box the word "probable" should be used in preference to "possible." Almost anything is possible, but the court wishes for information on reasonable probability.

Evidence should be given in a voice which can be heard. In the county of Lancaster a speaker, to be considered adequate, must "stand up, speak up, and then shut up," and the same principle should apply to the courts. A witness must perforce stand up (unless prevented by physical disability), and he should certainly speak up. I have seen a calm court change quickly into a life-like representation of William Henley's "place of wrath and tears" because a medical witness would insist on muttering unintelligible technicalities in an inaudible tone. If we have anything to say which is worth hearing, let it be heard. The third point in the adequate speech—namely, a knowledge of when to stop—is equally important. In other words, simple affirmative or negative replies to questions are desirable whenever possible, though at times it is necessary to add some such words as these: "I should, however, like to qualify this by saying. . . ." Any witness who makes a long and rambling reply to a question is laying up trouble for himself and his case.

I think that no one will deny that there is a psychological background for the nervous disorders which may follow injury. Can we, as medical witnesses, hope to make such an approach intelligible in plain language when we are giving evidence? I can imagine the most urbane of His Majesty's judges dealing forcefully with a doctor who attempted to harangue the court on the relative merits of various schools of thought in psychology. But it is surely possible to explain that the mental make-up of the individual, and the influences which have been active since his earliest days, have had an effect on his outlook as regards his injury. Such a statement could only be regarded as sound common sense, but the viewpoint is one which has been in the past, and frequently still is, insufficiently stressed.

Summary

A series of 400 compensation cases is reviewed, and the proportion of those in which functional nervous disorder developed subsequently is given.

Factors in the causation of these disorders are discussed, and a classification of such disorders is put forward.

Views are expressed on prognosis and treatment in these cases.

The paper refers, in conclusion, to the legal aspect from the standpoint of the medical witness.

I wish to acknowledge with gratitude my indebtedness to Sir James Purves-Stewart's well-known book, *The Diagnosis of Nervous Diseases*, from which many quotations have been made in this paper.

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THE STRUCTURE AND FUNCTIONS OF SYNOVIAL MEMBRANE AND ARTICULAR CARTILAGE*

BY

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John Hunter taught us the need for accurate anatomical and physiological knowledge as a basis for the rational treatment of injury and disease. The result of neglect of this principle is demonstrated by the present unsatisfactory position relating to rheumatic diseases, particularly as they affect the joints. It has been estimated that in the United Kingdom alone there are more than a million adults and more than 200,000 children who are suffering from rheumatic disease, both articular and non-articular, and it is probable that this number exceeds the combined total of those suffering from heart disease, tuberculosis, and cancer. These disturbing facts should stimulate further interest in the neglected subject of the anatomy and physiology of joints and of other structures liable to be attacked by rheumatism. In fact, we must replace the shifting sands upon which much of our treatment of rheumatism is at present based by a firmer foundation built upon Hunterian principles. Such principles are also of vital importance in the treatment of injuries of joints, if prolonged or even permanent disability is to be avoided and the menace of unqualified practice in this sphere removed.

It is impossible within the scope of a short paper to deal adequately with such a large subject, and as a basis of discussion I propose to discuss these problems under two principal headings: (a) the structure and functions of synovial membrane; (b) the structure and functions of articular cartilage.

Structure and Functions of Synovial Membrane

During the development of a diarthrodial joint a splitting of the undifferentiated mesenchyme occurs, the central part becoming the articular cartilages and interarticular fibrocartilages when present, and the lateral portion the synovial membrane, capsule, and its accessory ligaments. This mesenchymatous origin of the different elements of the joint explains the readiness with which under certain conditions, as in osteo-arthritis, cartilage and bone develop in the synovial membrane, or with which the articular cartilage and interarticular cartilages may be transformed into connective tissue or bone. It was formerly considered that the synovial membrane of a joint forms a closed sac which completely covers the inner surface of the capsule and the surfaces of the articular cartilages. It is now established, however, that the synovial membrane resembles rather a sleeve with two surfaces and two circumferences, the latter being attached to the margins of the articular cartilages, where, to the naked eye, they appear to end. Microscopically, however, the synovial membrane can be traced for a short distance over the extreme lateral part of the articular cartilage. In the same manner, such intra-articular fibrocartilages as the semilunar cartilages in the knee-joint are not completely clothed by synovial membrane, as was at one time thought, for the membrane strays for a short distance

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only over the peripheral portions. I have endeavoured to demonstrate that this relation of the synovial membrane to the articular cartilage explains much that has hitherto been obscure in the pathology of osteo-arthritis, and that the relation of the membrane to the semilunar cartilages of the knee-joint is of great importance in regard to injuries of the menisci and their treatment.

Structure

A typical synovial membrane consists of an outer layer of lax connective tissue continuous with the joint capsule, and an inner layer which is in the main smooth and shining like such serous membranes as the pleura or pericardium. Near the articular margins the membrane is studded with villi, which are enlarged and more numerous in many forms of synovitis or arthritis. This arrangement of the villi enables their secretion to be readily available to minimize articular friction.

The Non-villous Portion.—The structure of this part is by no means uniform. In those areas where the membrane is not subjected to much friction it is composed of a layer of flattened connective-tissue cells which form an endothelium-like surface, although neither in origin nor in structure are they true endothelial cells, as formerly considered. This layer of flattened cells rests upon one of lax connective tissue of areolar type containing both lymphatic and capillary plexuses, and between these layers a certain amount of gliding movement is possible. I pointed out the connective-tissue nature of this superficial non-villous layer in 1922, and among those who subsequently confirmed this observation were Key, Sabrazès, and Franceschini. The last-named has given the name "reticulo-endothelial" to this and also to the villous area of the synovial membrane, and considers that these portions possess the same functions as the reticulo-endothelial system possesses elsewhere. He does not believe that the underlying lymphatics have any *direct* connexion with the articular cavity. Where the non-villous area of the synovial membrane is subjected to friction—as, for instance, where it covers the deep surface of the tendon of the quadriceps extensor in the knee-joint—the above-mentioned endothelium-like layer is absent and is replaced by a collagenous layer, the fibrils of which run parallel to the underlying tendon. In this collagenous layer are embedded connective-tissue cells which also lie parallel to the surface. This portion of the synovial membrane contains comparatively few blood vessels.

The Villous Portion.—The villi are invested by rounded or oval cells of the connective-tissue type with prominent spherical or oval nuclei. In the stem of the villus these cells are disposed in a single layer, but near the extremity they lie in three or four layers, especially when there is a condition of synovitis. The function of these cells is the secretion of synovia. In 1922 I found that, on staining synovial villi with carbol-thionin, globules of mucin could be demonstrated in these synovial cells together with the granules from which they were derived. These were independently described by Mayeda at the same time and subsequently confirmed by Sabrazès and Kling. Certain fatty processes that project into joint cavities, such as the infrapatellar pad of fat in the knee-joint, are so richly supplied with synovial cells that the name "synovial glands" given to these processes by Clopton Havers receives histological justification. The mechanical pressure of the joint movement upon these processes expels the mucin from the synovial cells into the cavity of the joint.

Regeneration of Synovial Membrane.—It has been found that if large areas of the synovial membrane are

removed in experimental animals or by operation in human beings a new membrane is formed by metaplasia of the cells of the subsynovial tissues that is indistinguishable from that normally present. A similar phenomenon is observed in false joints.

Synovial Fluid

Many problems concerning the synovial fluid are still obscure, and further research is needed to rectify the gaps in our knowledge. Opinions differ concerning whether it is a transudate, a secretion, or a product of disintegration. It is probable that all these factors play a part in its production.

Normal Composition.—Analysis of human synovial fluid from a personal series of cases showed that the total solids averaged 4.41 per cent., of which the protein content averaged 1.6 per cent. and the mucin content 1.95 per cent. It has been estimated that the protein content of the lymph in the thoracic duct varies from 3.5 to 4.3 per cent. and that of the lymph from the limbs is 2.4 per cent. It seems clear from these analyses not only that synovial fluid contains a high percentage of mucin but that the protein content is lower than that of the lymph. Does not this show that the principal function of the synovial fluid is that of a lubricant by virtue of the secretion of mucin by specialized synovial cells, and that the part it plays in nutrition by transudation of lymph from the subsynovial capillaries is comparatively unimportant? I propose to revert to the element of disintegration later when discussing the articular cartilage.

Experimental Work upon Absorption from Articular Cavities

Space will permit only a cursory examination of this problem. Diffusible substances pass readily from the blood to the synovial fluid, and vice versa. Cajori, Pemberton, and others have shown, for instance, that it is possible to detect glucose in the synovial fluid half an hour after oral administration, and Key has shown that diffusible dyes such as trypan-blue, when injected intravenously in rabbits, rapidly stain the synovial fluid. The actual mode of absorption from the joint cavity is still undecided, and more certain knowledge is long overdue. It has been shown by Le Gros Clark that when trypan-blue is injected into a joint the particles are taken up by the synovial cells, which then migrate into the subsynovial layer. No appreciable absorption took place until twelve hours had elapsed, and he argued that the synovial membrane formed a closed sac and that there could be no question of loose connective-tissue spaces abutting upon the joint cavity. It seems highly probable that the synovial cells are able to deal in this manner with foreign particles.

In my own experiments I found that absorption of isotonic solutions or diffusible dyes took place rapidly, and I endeavoured to show that such absorption was mainly by the subsynovial capillaries. Colloidal dyes of greater molecular composition which approximate more closely to the synovial fluid were absorbed more slowly by the subsynovial lymphatics. *It was found that in both types absorption took place more rapidly when movements of the joint of the experimental animal were permitted.* Early movement in injuries and diseases of joints associated with a plastic synovial exudate would appear, therefore, to be the best way of avoiding adhesion formation and prolonged disability. The rapidity with which substances pass from the blood to the synovial fluid, and vice versa, seems to indicate that the synovial membrane

is not a completely closed sac and that there is ready access in certain areas to the lymphatics and capillaries.

The Structure and Functions of Articular Cartilage

The problems of the aetiology and pathology of arthritis, particularly of the osteo-arthritic type, are intimately connected with the structure and function of articular cartilage. This tissue is, as we have seen, of mesenchymatous origin and is well adapted for the functions it performs. When in health, it has a smooth surface which is lubricated by the synovial fluid, whereby friction is reduced to a minimum. It is of great strength and resiliency, and thus serves to protect the subjacent bone.

I shall endeavour to make clear that there are important differences in structure and function between the central and lateral areas of articular cartilage, and that these fundamental facts afford a simple explanation of much that was previously puzzling and obscure in osteo-arthritis. From the systematic examination of sections of articular cartilage at different ages it has been found that degenerative changes begin there at a much earlier age than was hitherto supposed. These age-changes in the tissues of the body, starting as they do often at different periods of life, are of great anatomical, physiological, and pathological interest. I was able to show by systematic post-mortem examination of a large number of joints that in over 90 per cent. of all persons between 60 and 70 fibrillation of the central articular area visible to the naked eye was present, and Bauer and Bennett have since demonstrated by microscopical investigation that degeneration of this central zone actually begins in the third decade of life.

Central Area of Articular Cartilage

If the actual surface of this area be examined microscopically it will be seen that it is constituted by a well-defined and clear-cut margin which is devoid of any cell covering or perichondrium and is evidently formed of collagenous matrix. A delicate layer of cells constituting a perichondrium has been described by some previous workers, but I have not been able to confirm this in normal adult articular cartilage, although it unquestionably exists at an early stage of development. In this superficial stratum of the articular cartilage, and embedded in the matrix, can be seen a few layers of flattened cartilage cells arranged in groups of two to four cells which lie parallel to the surface. A point which I wish to emphasize is that the cartilage cells near the surface show no sign of degeneracy. In the intermediate zone of the articular cartilage the groups of cells are more irregularly disposed, and in the deeper zone the cells are arranged vertically. Where the deeper portion of the matrix lies upon the subarticular layer of bone it is infiltrated by a deposit of lime salts.

The usually accepted view of the structure and function of articular cartilage is based upon the teaching of Ogston. He maintained that articular cartilage is continually renewing itself from a focus of *central* growth, and that it develops in the direction of the joint an effete layer which is worn away by the joint movements and participates in the formation of the synovial fluid. He further maintained that the cells in the deeper zone, also formed from this focus of central growth, fulfilled the function of reproducing the subarticular layer of bone. It is difficult to believe that Ogston's investigations were carried out upon normal articular cartilage. It seems clear that

instead of being degenerate the superficial cells of the articular cartilage are the source from which the deeper cells are derived, and that they are analogous to the superficial cells of the lateral portion of the articular cartilage or to the perichondrial cells of other varieties of hyaline cartilage. It is probable, however, that a certain amount of disintegration of the superficial collagenous layer may occur and contribute to a slight degree to the synovial fluid.

It appears to be the case that the deeper layer of cartilage cells are in fact dying cells, and a slow process of absorption of these cells takes place by vascular inroads containing chondroclasts from the subjacent bone. This process is very greatly increased in osteo-arthritis.

Lateral Area of Articular Cartilage

This area resembles those varieties of hyaline cartilage, such as costal cartilage, which are furnished with a perichondrium, for its surface is covered by a delicate extension of the synovial membrane. When traced centrewards, the connective tissue is reduced to a single layer of close-set endothelial cells; these subsequently produce hyaline matrix, in which they become buried, so that the more central parts of the articular cartilage, as we have seen, exist at the free surface of matrix. At the edge the articular cartilage becomes greatly fibrillated and merges into fibrous tissue, beyond which it is furnished with capillaries derived from the *circulus articuli vasculosus*. In the thin synovial layer upon the surface lie capillaries derived from the *circulus*, and blood vessels can also be traced from the subarticular layer of bone into the deeper layer of this part of the cartilage. It is important, therefore, to bear in mind that this lateral portion of the articular cartilage is far better nourished than the central portion. This fact has a most important bearing upon the joint changes that occur in osteo-arthritis.

This difference in structure of the central and lateral portions of the articular cartilage is capable of explanation on developmental grounds, and a study of comparative anatomy is instructive because it shows that certain animals preserve, throughout life, the stages that characterize human articular cartilage at early developmental stages.

Nutrition of Articular Cartilage

According to William Hunter articular cartilage derives its principal nutrition from the *circulus articuli vasculosus*. Toynbee assigned to the subarticular vessels the most important role. Some workers, including Strangeways, have argued that the synovial fluid plays an important part in nourishing the cartilage, pointing to the continued growth of loose bodies composed of cartilage. However, there can be no doubt that the presence of a loose body is associated with synovitis with a synovial fluid enriched by inflammatory exudate. The analyses of normal synovial fluid mentioned above reveal such a low percentage of albumin that there can be little doubt that the nutritional role of synovial fluid is of minor importance. I have observed that an injection of carmine and gelatin into the circulation readily permeates the subarticular osseous layer and that, not infrequently, blood vessels can be traced through this layer into the deeper layers of the articular cartilage.

To summarize, it appears probable that the principal source of nutrition of articular cartilage is the *circulus articuli vasculosus*, and that this is supplemented (*a*) by the synovial fluid, which assists in nourishing the super-

ficial and more central zone, and (b) by the subarticular vessels, which assist in nourishing the deeper zone.

How does the nutrient fluid gain access to the cartilage cells? No lymphatics have ever been demonstrated in articular cartilage. If, however, a section be examined that has been stained by carbol-thionin, which stains mucin pink, it will be seen that the zone of matrix immediately surrounding the cell groups is clearly mucinous and the most recently formed portion. It will be found that these pink or mucinous zones branch, intercommunicate, and form a sponge-like structure around the meshes of which lie the older or collagenous portions of the matrix, and it is probable that the cartilage is nourished by plasma that percolates along this mucinous network.

Repair in Articular Cartilage

As the central and superficial area of the articular cartilage is nourished principally by the synovial fluid, which, as we have seen, has a low protein content, and the lateral areas are nourished by the circulus articulari vasculosus, it is not surprising to find a difference in the response of these different zones to both injury and disease. To ascertain this I performed a series of experiments. In the first, incisions were made in the central and lateral areas of the articular cartilage in rabbits. The findings of Redfern were confirmed—namely, that incisions in the central portion remained unhealed for long periods, and that if repair took place eventually the bond of union was of connective tissue derived from a feeble proliferation of the cartilage cells at the margin of the incision. Incisions in the lateral portions, however, healed more rapidly, and there was a new formation of cartilage by active proliferation of the cartilage cells in which the perichondrium participated.

Experimental Production of Osteo-arthritis

In a further series of experiments it was found that removal of the central poorly nourished area of the articular cartilage was followed by compensatory proliferation of the lateral better-nourished areas, and I am of the opinion that the chondro-osteophytes, which are such a prominent feature in osteo-arthritis, are often due to compensatory proliferation of the lateral articular areas after destruction by injury or disease of the central areas. In arthritis arising from toxins it is possible that those toxins that cause destruction of the poorly nourished areas may bring about proliferation of the better-nourished lateral zones.

It is clear that an urgent need exists for further research into the neglected subject of the anatomy and physiology of joints.

Summary

The structure and functions of synovial membrane and of articular cartilage are discussed in their relation to the treatment of rheumatism and injuries to joints.

The relation of synovial membrane to articular cartilage is explained.

The result of an analysis of synovial fluid is given and its principal function discussed.

A brief examination of the problem of absorption from articular cavities is made.

Differences in structure and function between central and lateral areas of articular cartilage are reviewed in their bearing on osteo-arthritis.

The source of the nutrition of articular cartilage is discussed, together with the manner of repair.

THE RELATION OF THE ANTERIOR PITUITARY GLAND TO CARBO- HYDRATE METABOLISM*

BY

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Since the first clinical observations were made concerning the frequency with which glycosuria occurs in cases of pituitary tumour (Loeb, 1884) much experimental evidence has accumulated to show that the pituitary gland plays an important part in the control of carbohydrate metabolism. The early experimental investigations (Borchardt, 1908; Cushing, 1912) stressed the significance of the posterior pituitary lobe in this connexion, but the fundamentally important researches of B. A. Houssay and his collaborators have now turned our attention to the anterior lobe of the pituitary gland. Although the possibility cannot be entirely ruled out that secretions of the posterior lobe influence carbohydrate metabolism, at present the anterior portion of the pituitary gland is believed to be of greater significance in this respect. The evidence for this belief emerged in a striking manner from the investigations of Houssay and his colleagues.

In 1924 Houssay and Magenta found that dogs from which the pituitary gland had been removed were excessively sensitive to the toxic action of insulin. In agreement with the prevailing views, this increase in sensitivity to the action of insulin was believed to be due to removal of the posterior portion rather than to removal of the anterior lobe of the hypophysis, an assumption which was apparently supported by the findings of Geiling, Campbell, and Ishikawa (1927).

In the toad removal of the pars glandularis of the pituitary gland (corresponding with the anterior lobe in mammals, although it is somewhat posterior in this species) can be effected with greater ease than in mammals, and Houssay and Potick (1929) investigated the influence of the removal of the whole pituitary gland, and of the pars glandularis only, on the insulin sensitivity of the toad. They were surprised to find that extirpation of the pars glandularis alone greatly increased the sensitivity of the animal to insulin, and that subcutaneous daily grafts of toad pars glandularis counteracted this excessive sensitivity of the hypophysectomized toad to the hypoglycaemic action of insulin, although similar grafts of tissue from pars nervosa (including tissue from pars intermedia) were ineffective. These experiments demonstrated that the pars glandularis was that part of the pituitary gland largely or solely concerned with the regulation of the sensitivity of the toad to the hypoglycaemic action of insulin. Similar results have more recently been obtained with mammals (Pencharz, Cori, and Russell, 1936; Swann and Fitzgerald, 1938), and it is now concluded that in all species the secretions of the anterior lobe, rather than those of the posterior lobe, are of importance in the regulation of insulin sensitivity.

If, as demonstrated by Houssay and Potick, the secretions of the pituitary gland are active in inhibiting the action of insulin, then it might be expected that removal of this gland would diminish the intensity of a diabetic condition. Houssay and Biasotti (1930) found that in the

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