I understand that similar cases of bent back are not very rare in workmen after accidents, but they have always proved very resistant to treatment. Perhaps the use of the board described in this paper will in the future afford a rapid means of curing civilians as well as soldiers.

REFERENCES.

- ¹ Souques and Mdle. Rosanoff-Saloff: *Rev. Neur.*, xlii, 937, 1915.
² Laignel-Lavastine and P. Courbon: *Revue Générale de Pathologie de Guerre*, p. 1, Paris 1918. ³ J. A. Sicard: *Bull. et mèm. de la Soc. Méd. des Hôp. de Paris*, xxxix, 582, 1915.

Some Remarks

ON THE

MORBID ANATOMY AND HISTOLOGY OF
RHEUMATOID ARTHRITIS.*

[WITH SPECIAL PLATE.]

BY

T. P. S. STRANGEWAYS,

LECTURER IN SPECIAL PATHOLOGY IN THE UNIVERSITY OF CAMBRIDGE
(From the Laboratory of the Cambridge Research Hospital.)

THE following is a summary of a report giving a detailed description of the changes found in joints of patients suffering from that form of chronic arthritis at present recognized clinically as rheumatoid arthritis. The report referred to was submitted to the Medical Research Committee, which made a generous grant in aid of the work from the funds at their disposal.

Most of the specimens which furnished the material for the report were obtained during *post mortem* examination of over 2,000 joints of patients suffering from one or the other of the following forms of chronic arthritis—namely, rheumatoid arthritis, osteo-arthritis, chronic gout, or Charcot's disease. I am indebted to a large number of doctors in practice in Great Britain and Ireland for the clinical and pathological material from which this report was prepared, and I wish to express my gratitude to them for allowing me to conduct the necessary *post mortem* examinations. The anatomical and microscopical specimens prepared to demonstrate the various changes in such joints are preserved at the Cambridge Research Hospital, where they are accessible for inspection to any interested. The revised summary here given has been written in the form of categorical statements.

The term "rheumatoid arthritis" as at present used includes several forms of arthritis which are clearly due to different causes, although clinically they may show several points of similarity.

The crippling and deformity associated with rheumatoid arthritis, or what is taken as such, are largely of muscular origin, which may be (a) of the nature of an involuntary contraction brought about by pain referred to the joint of the crippled limb; (b) due to an involuntary muscular spasm caused by pain on movement of the damaged joint; (c) due to actual atrophy and shortening of some of the muscles connected with the diseased joint. This atrophy is usually associated with disuse and long-continued muscular spasm.

In other cases the deformity is due to changes in the joint itself, such as (a) distension of the capsule by an excess of synovial fluid; (b) dislocation of the bones of the articulation; (c) changes in the shape of the articular surfaces owing to formation of new bone or to erosion of the original.

Some joints which clinically appear to be damaged show very little morbid change on *post-mortem* examination, although symptoms of arthritis with crippling deformity have been present for many years.

Cases are observed in which the capsule of the joint has been distended for a long period by an excess of synovial fluid, accompanied by more or less deformity, but in which on *post-mortem* examination no marked changes are discovered. In some examples of this type the fluid ultimately diminishes. Fibrotic changes may then be present in the capsule, and the articular cartilages may have undergone fibrillation or atrophy.

A considerable proportion of the joints show distinct inflammatory changes in the synovial membrane, in the capsule, or in the bones of the articulation; in any joint

the articular cartilage may be also involved. These inflammatory lesions may be present in one or all of the above mentioned structures, and be either acute, subacute, or chronic.

In a few cases the processes are obviously of infective origin, and are associated with marked inflammatory changes in the synovial membrane and the formation of thick fleshy villi, and vascular adhesions. Microscopically the inflamed tissues show large collections of inflammatory cells and new capillaries. Erosion of the articular cartilage and bones may also be present.

The changes found in a joint affected with what is termed rheumatoid arthritis are usually of an inflammatory nature, but their severity and extent vary considerably in different cases and in different joints from the same case. The changes may be present in a part only of the articulation.

The inflammatory process may originate either in the synovial membrane, in the capsule, or in the superficial cancellous spaces of the epiphysis, or in all three of these structures.

The inflammatory process, if severe, is associated with proliferation of the connective tissue cells, the development of new blood vessels, the accumulation of leucocytes, and sometimes with the extravasation of red blood corpuscles. The inflammatory tissue may originate in the synovial membrane or in the capsule and invade the articular cartilage and bone, or lead to the formation of inflammatory adhesions in the joint cavity. This inflammatory tissue tends in the course of time to become organized and converted into fibrous tissue and may bring about fibrous ankylosis either between the adjacent surfaces of the capsule or between the cartilage, or even between the bones of the articulation if the original cartilage has been destroyed.

In some cases the arthritis is of a subacute type from the onset and the inflammatory changes, although often progressive, are not so marked. In this type the changes may originate in the synovial membrane (Fig. 1), the capsule or the superficial marrow spaces of the epiphysis, from any of which they may spread to the articular cartilage; the process leads to the formation of fibrosing tissue in the affected areas, and this, when present in the capsule, causes the latter to contract. The movements of the limb are in consequence restricted, and the articular cavity decreased in size. Fibrous adhesions also develop in these joints, and in some cases fibrous, cartilaginous (Fig. 6), or bony ankylosis.

The changes in the superficial marrow spaces lead to resorption or erosion of the osseous trabeculae, which may be associated with the invasion and replacement of the articular cartilage by the inflammatory tissue (Fig. 5).

Other joints show a slowly progressive inflammatory fibrosis of the capsule often associated with degenerative changes in the cartilage and proliferative changes in some of the superficial marrow spaces. In these joints areas of cartilage may be invaded, either superficially from the capsule, or from beneath from the superficial marrow spaces.

The inflammatory reaction of the marrow of the superficial cancellous spaces of the epiphysis may be of an acute, subacute, or chronic type. In any type the connective tissue cells of the marrow proliferate and new blood vessels form. In many specimens the new connective tissue cells are of stellate form. In other specimens the connective tissue cells appear more fibroblastic, especially such as be near the edges of the bone trabeculae, but in all cases these cells show a tendency to form adipose tissue as the inflammatory process subsides. In those cases where the superficial osseous trabeculae are eroded and the zone of calcified cartilage invaded, the connective tissue cells and vessels form a definitely organized fibrotic tissue, the cells of which do not show the same tendency to form adipose tissue.

In no instance has it been possible to demonstrate periarticular changes of an inflammatory nature around the affected joints, and it is doubtful if there is such a condition as periarticular rheumatoid arthritis.

The changes in the cartilage vary considerably in different joints from the same case, and even in the same joint.

The articular cartilage may show signs of atrophy accompanied by modifications in the staining reaction of the matrix.

* Read at a meeting of the Medical Society of London, October 28th, 1918.

The articular cartilage may show proliferation of its cells which results in the formation of cell groups usually surrounded by an unstained zone.

The cartilage may become definitely fibrillated, and with this change there is usually evidence of proliferation and the formation of groups of cartilage cells (Fig. 2). The fibrillation begins as a rule on the free surface, and may extend to the deepest parts of the articular cartilage.

The hyaline cartilage may become converted into a modified fibro-cartilage, but in such specimens there is usually evidence of some inflammatory process in the neighbourhood of the altered structure. This process seems to be due to proliferation of the cartilage cells, but in some specimens the connective tissue cells of the inflammatory tissue also appear to take part in the formation of fibro-cartilage.

Areas of the articular cartilage may become necrotic; this necrosis may be found where inflammatory reaction has taken place. The edges of the necrotic mass often show a beautiful "replacement fibrosis" (Fig. 3), which may eventually lead to the complete removal of the necrotic tissue.

In some joints portions or even the whole layer of the articular cartilage may be infiltrated and replaced by a more or less vascular inflammatory tissue (Fig. 4) owing to the cartilage having been invaded by new blood vessels and connective tissue cells. In certain specimens the cartilage cells proliferate, and appear to take part in the formation of the new tissue which has replaced the cartilage (Fig. 4). This replacement of cartilage may begin either on the free surface from an inflammatory process spreading from the synovial membrane or capsule, or in the deeper parts of the cartilage by the extension of an inflammatory process from the subjacent marrow spaces (Fig. 5).

The articular bone may show atrophy, rarefaction, resorption, or erosion.

The superficial osseous trabeculae underlying those portions of the articular surface in which advanced atrophy, fibrillation, or complete wearing away of the cartilage has taken place often show increase in size and density owing to the formation of new bone, brought about by continued use of the limb notwithstanding the joint changes. The amount of the new bone formed appears to depend upon the reaction of the tissues to pressure, and this increases in proportion to the weight and friction on the affected area. In those instances where the cartilage is absent and the superficial bone exposed this process leads to polishing of the superficial surface of the sclerosed bone. Associated with this increased density of the osseous trabeculae minute fractures are often seen; these are probably of traumatic origin. In the neighbourhood of these fractures there is generally callus formation with a combined process of resorption and repair around the injured area. These changes are common in osteo-arthritis and chronic gout, but are not common in rheumatoid arthritis.

In those instances in which the inflammatory changes are confined to the synovial membrane active changes are not observed in the bone marrow or osseous trabeculae, but there is often atrophy of the osseous trabeculae in the neighbourhood of the affected joint; this appears to be due to disuse.

When an inflammatory process attacks the articular cartilage, or bone of a joint, inflammatory changes do not, except in rare instances, involve the whole of the epiphysis, but are usually strictly confined to the quite superficial cancellous spaces and superficial osseous trabeculae (Fig. 5). As a rule these changes are not found over the whole of the articular surface, but only in isolated areas; they vary greatly in intensity and extent in different joints or in different parts of the same joint. The process may be a chronic, slowly progressive resorption of bone accompanied by new formation of bone in the neighbourhood. In such areas very few or no multinucleated osteoclasts are observed. When the process is more active, proliferative changes are found in the bone marrow with congested blood vessels, multinucleated osteoclasts, and inflammatory cells. This process often leads to erosion of the articular cartilage and the underlying bone; with very rare exceptions the formation of new bone can be seen taking place in the affected area. In some cases the resorption of bone is more rapid than the new formation, in others formation of new bone is in excess, and may lead to the formation of bony outgrowths on or around the articular surface.

The development of new bone in a damaged joint may take place (a) in the articular cartilage, (b) in altered articular cartilage, (c) in the zone of calcified cartilage, (d) on the edge of pre-existing bone trabeculae, (e) in inflammatory connective tissue in the cancellous spaces, (f) in fibrous adhesions.

The development of new bone in hyaline cartilage may be due to changes in the cartilage cells; these changes are usually preceded by a deposition of calcium salts in the surrounding matrix. This is followed by proliferative changes in the cells and the gradual development of new bone around the modified cartilage cells.

The development of new bone in altered hyaline cartilage—for example, fibro-cartilage—may occur through changes similar to those described in the hyaline.

The development of new bone is sometimes seen in areas of vascular inflammatory tissue which have invaded and replaced a portion of the articular cartilage. The new bone in this case may either be formed by cartilage cells as above described, or from the fibroblastic cells of the inflammatory tissue.

The development of new bone in the zone of calcified cartilage may be due to changes similar to those described in the hyaline.

In rheumatoid arthritis the development of new bone on the edges of pre-existing bone trabeculae is usually accompanied by proliferative changes in the marrow, which lead to resorption of bone in the neighbourhood of the new formation. The two processes occur simultaneously, and appear to depend upon some irritant causing increased blood supply, which brings about resorption, and upon pressure on the affected area from use of the limb, which causes the development of new bone.

When new bone develops in inflammatory tissue which has replaced the marrow and osseous trabeculae it appears to be formed from fibroblastic cells in this inflammatory tissue.

New bone in fibrous adhesions appears to be formed from the fibroblastic cells of the fibrous tissue.

In all the above instances the development of new bone is associated with the formation of cancellous spaces and marrow tissue. The new marrow usually consists of adipose tissue. The formation of the cancellous spaces appears to be due to the development of new blood vessels, to changes in the vascular supply, and to the development of stellate connective tissue cells which ultimately form adipose tissue.

Limitation of movement in a joint may be due to (a) muscular spasm, (b) shortening and atrophy of muscles and tendons, (c) fibrotic changes in the capsule leading to contraction, (d) alteration in shape of the articular surfaces, (e) ankylosis which may be fibrous, cartilaginous, or osseous.

Where the limitation of movement in a joint is due to muscular spasm it can be overcome by deep anaesthesia, but it returns when the effect of the anaesthetic has passed off.

The forcible movement of a joint in which shortening and contraction of the muscles and tendons is suspected should not be lightly undertaken, as it is often associated with fatty changes in all the tissues of the joint, and fracture of any or all the tissues around the joint may take place.

Fibrotic changes in the capsule associated with contraction may be so extreme that the joint cavity is completely obliterated and the joint surfaces lie in close contact with the fibrous capsule moulded tightly around the articulation.

Fibrous ankylosis is due to adhesions formed by the organization of inflammatory tissue which may originate either in the synovial membrane, the capsule, or in the superficial marrow spaces. These adhesions may partly or completely occlude the joint cavity. They may consist of long processes of more or less vascular fibrous tissue, which thus allow limited movement to take place in the joint, or of dense contracted fibrous tissue which firmly unites the articular surfaces of the two bones (fibrous ankylosis).

The articular cartilage may become ankylosed by the matrix of the two layers of the hyaline cartilage becoming fused into one continuous layer, or the two layers may unite and be transformed into a modified fibro-cartilage (Fig. 6). The ankylosed cartilage may be

FIG. 1.—Showing inflammatory changes in the synovial membrane and capsule. *a*, Synovial membrane. *b*, Group of inflammatory cells. *c*, Thickened blood vessel.

FIG. 2.—Showing fibrillation of articular cartilage. *a*, Group of proliferated cartilage cells. *b*, Fibrillation of cartilage. *c*, Superficial bone trabeculae. *d*, Marrow.

FIG. 3.—Showing replacement fibrosis of necrotic hyaline cartilage. *a*, Necrotic cartilage. *b*, Fibroblasts invading necrotic cartilage. *c*, Multinucleated cell. *d*, Young blood vessel.

FIG. 4.—Showing inflammatory tissue invading surface of articular cartilage. *a*, Articular cartilage. *b*, Inflammatory tissue. *c*, Superficial bone trabeculae. *d*, Blood vessels and inflammatory cells. *e*, Cartilage cells which appear to be taking part in the formation of the fibrous tissue.

FIG. 5.—Showing inflammatory tissue from the superficial marrow spaces invading and replacing deeper layers of articular cartilage. *a*, Superficial marrow space. *b*, Group of inflammatory cells. *c*, Inflammatory tissue replacing cartilage. *d*, Young blood vessel. *e*, Superficial layer of articular cartilage.

FIG. 6.—Showing ankylosis due to inflammatory changes. *a*, Newly formed bone. *b*, Ankylosed hyaline cartilage. *c*, Ankylosed fibro-cartilage. *d*, Young connective tissue cells and new blood vessels. *e*, Group of inflammatory cells.

invaded and replaced by an inflammatory fibrous tissue (Fig. 6, d) or new bone may develop in the ankylosed cartilage and thus bring about osseous ankylosis.

Osseous ankylosis takes places by the development of new bone either in ankylosed cartilage or in the fibrous tissue which has already produced fibrous ankylosis.

Ankylosis may occur between the two zones of calcified cartilage, but this form of fusion shows a tendency to become replaced by one of true bone.

Villous outgrowths are found in some joints. These may be due to (a) overgrowth of normal villi; (b) inflammatory changes in the synovial membrane or in the capsule.

Villous outgrowths in a joint may consist of (a) vascular fibrous tissue, (b) dense fibrous tissue, (c) fibrous tissue enclosing groups of fat cells, (d) inflammatory tissue with dilated capillaries and groups of inflammatory cells, (e) degenerated or necrotic tissue, (f) connective tissue showing vessels deeply congested owing to obstructed circulation.

Villous outgrowths may become detached by rupture of the fine pedicles, and so form a loose body in the joint cavity. The detachment may be preceded by necrosis.

Microscopic villi formed of cartilage are occasionally found on the surface of altered articular cartilage. These may be formed of hyaline or fibro-cartilage.

No constant changes are found after death in the organs or tissues of patients who have suffered from rheumatoid arthritis.

OBSERVATIONS ON THE CAUSE OF RICKETS.

[WITH SPECIAL PLATE.]

BY

D. NOËL PATON, LEONARD FINDLAY,

AND

ALEXANDER WATSON.

(From the Physiological Laboratory, University of Glasgow.)

In the course of an investigation on metabolism in rickets the difficulty of getting satisfactory material from children induced us to produce rickets in a certain number of young dogs, while keeping others free from the disease.

The previous experiences in this laboratory had shown that rickets may almost certainly be induced in the great majority of pups of certain breeds of dog by simply keeping them in the animal house of the department, while the experience of every keeper who breeds dogs is that if pups are to be reared without rickets developing they must have abundant exercise in the open air. One of us (L. F.) has already published an experimental investigation on the etiology of rickets in young dogs,¹ in which he records that puppies freely exercised when fed on bread and water, oatmeal and water, etc., did not develop rickets, but became marasmic and died. On the other hand, puppies fed on oatmeal porridge and milk, if allowed to run about, remained free of the disease, but if confined developed it.

In the large series of experiments made by Mills Renton and Madge Robertson² in this laboratory on the influence of thymusectomy on the production of rickets, all the pups were kept on the same diet of oatmeal porridge and milk with bones for them to gnaw. Some became rickety, some remained free of the disease, their immunity seeming to depend rather upon the breed than upon their mode of life. Thus, all the collies developed rickets; of the retrievers one remained normal while two became rachitic; the two fox terriers showed slight signs of rickets, while the two greyhounds remained normal. Thymusectomy had no effect on the onset of the disease. One collie which had suffered severely from rickets made a complete recovery, and was alive and well except for deformities at the age of six months. The diet had not been altered, but the animal had been kept outside during August and September for most of each fine day.

In 1913 Casimir Funk³ suggested that rickets may be due to absence of some "vitamine" from the food, but his arguments in favour of this view are far from convincing.

As is well known, Bland-Sutton maintained that by the administration of fat the development of rickets in young carnivores kept in confinement might be prevented. But the general experience of zoological gardens at present is that no amount of fat in the food will prevent rickets if the cubs are confined.

Hess and Unger⁴ record observations on negro children in the negro quarter of New York where a very high proportion develop rickets, which tend to show that cod-liver oil has a prophylactic action.

E. Mellanby, on January 26th, 1913, gave a short communication to the Physiological Society reviving Funk's vitamine theory and maintaining that he had demonstrated by experiments on pups that—

"1. Rickets is a condition primarily due to lack of an accessory factor in the diet.

"2. This accessory factor is found in (1) extractives, especially meat; (2) fats, especially butter, but not in linseed oil.

"3. Lack of exercise may play some part, but not a primary part, in the development."

Till his evidence has been published it is of course impossible to estimate the value of the observations. The present vogue of "vitamines" and "accessory factors" seems to have led to a somewhat premature adoption of this theory.

The very extensive study of the "Social and Economic Factors in the Causation of Rickets" by Margaret Ferguson from this laboratory⁵ gives little support to the theory that the disease is due to a dietary deficiency. The tables given on pp. 68 and 69 seem to show conclusively that the difference in diet between rachitic and non-rachitic families is small and that the overlap is large, and indicate pretty clearly that some other factor than feeding is involved in the causation of the condition. The very striking difference in the air space of the houses and in the extent to which the two groups of children had opportunities of free egress to the open air seems to show that in some way these conditions exercise a marked influence upon the immunity to the development of rickets.

Present Observations.

As already stated, the present observations were not undertaken primarily to investigate the etiology of the disease, but to give us a certain number of normal controls, and a certain number of rachitic animals for the study of calcium metabolism.

Since seventeen pups were involved an opportunity was afforded of checking and extending our previous experience.

Two litters were used, both collies, a breed peculiarly liable to rickets. The first litter of eight was received on March 30th, 1918, just after they had been weaned at seven weeks old. They were of a small black collie strain. When they arrived they were in poor condition and verminous. The vermin were destroyed, and they improved in condition. They were fed on oatmeal porridge and milk, and were killed at 13 weeks old.

The second litter of nine, of a rough working collie strain, were received with their mother on March 22nd, 1918, at 14 days old. They were all in good condition, and were suckled till about March 28th, and then put on oatmeal porridge and milk.

They were killed when about 11 weeks old.

A. Pups Sent to the Country.

Of the first litter a dog and a bitch were sent to the country on April 12th, 1918, when 9 weeks old. They were in poor condition when they left the laboratory. In the country they were kept in a large loose-box in a stable, and they had the run of a stable yard and garden under the personal observation of one of us (D. N. P.). They were sent back to the laboratory on May 12th and killed at the age of 13 weeks. They were strong and healthy and showed no signs of rickets. (Special plate, Fig. A.)

Of the remaining six of the first litter one was sent to the country on April 19th, 1918, in charge of another laboratory worker, but it did not get the same amount of exercise as the other four, and was returned on May 2nd, looking thin, after which it was allowed to run about in the laboratory. When killed at 13 weeks old the body was well nourished. X-ray and post-mortem examination failed to show definite signs of rickets at the ends of the bones, although the femur was soft and split easily with a knife.

Of the second litter a dog and a bitch were sent to the country on April 18th, 1918, at 5½ weeks old, and were kept under the same conditions as the first litters till June 3rd, when they were returned to the laboratory free of rickets and killed at the age of 11 weeks. Both sets of checks were fed upon oatmeal porridge and skimmed milk, the average amount consumed by each pup per day being: Oatmeal 150 grams, milk (skimmed) 280 c.cm. Taking the fat content of skim milk at even 1 per cent.—it is generally given at 0.3 per cent.—this gives 2.8 grams of fat per day.

B. Pups Kept in the Laboratory.

The remaining five of the first litter were kept in the laboratory in a large airy room. Four were as far as possible kept confined in a stall about 3 ft. by 3 ft.

One was allowed the run of the room, but being alone it took little exercise.

The food consisted of oatmeal porridge and whole milk—oatmeal 175 grams, milk (whole) 100 c.cm.—till May 21st, when.