Mobility with rigidity: a view of the spine*

Our backbone is traditionally the core and the guardian of our communications system. Built round the notochord and incorporating possibly still antigenic fragments of this archaic structure, dating back millions of years to the development of vertebrates in the littoral zones, the backbone is a supporting structure with forward-going, bilateral symmetry, a front and a back, a top and a bottom, and a left and a right, a witness to the past and also at the same time a firm basis for future progress (if we knew where we were going). Our spine is living evidence of our evolutionary vicissitudes and our determination to survive future ones, despite pollution, pullulation, politicians, profi-laciters, and last but not least ourselves.

Of the various tissue components of the spine cartilage is the most important, the matrix of growth. As man grows from 0 to 70 kg he must maintain his structure and function, and this is controlled by cartilage. Man starts as a jelly and ends as a stiff. The stiffness of old age is merely built-in obsolescence. Our bodies as discardable containers of the human spirit are a good deal better designed ecologically than the unbiodegradable plastic containers we are now littering over the world’s surface.

In prenatal life the spine must maintain its original marine mobility and at the same time the stiffness required by increasing size and later terrestrial life. This dual purpose, seemingly contradictory, is served by the interpolation of bony segments in the original cartilaginous tube. But we must remember that the bones are a secondary structure—a bit of stiffening, like whalebone in a corset (or in a whale).

Too many people have looked at the spine as a skeleton, a collection of dry bones, and surprisingly it is the bones that are named and numbered, not the discs. And yet what makes it more than a heap of old bones is the fibrocartilage of the discs. Now cartilage is regarded as a nonreactive tissue, but both its major constituents, collagen and chondromucoprotein, or proteoglycan, are potentially antigenic. It has a low, largely glycolytic, glucose-dependant metabolism and, at least in adult man, no blood supply, but it can keep out large molecules such as albumin or enzymes—the intramolecular excluded-volume effect—because of its coiled protein-polysaccharide content. It is nourished in the fetus by blood vessels and in child and adult by diffusion—both in disc cartilage and in the articular cartilage of diarthrodial joints. The ultimate source of growth and mobility is the chondrocyte, and many symposia have been dedicated to this apparently unsophisticated cell. This synthesises procollagen and secretes it into the matrix, where as collagen this triple helix forms the fibrillar framework. Its degradation probably depends on collagenase activated by other locally produced enzymes.

The chondrocyte also synthesises enzymes such as those in its lysosomes, cationic lysozyme occupying the lacunar space, probably also the matrix vesicles which may later initiate calcification and the proteoglycan hyaluronic acid complexes which are responsible for the rigidity of cartilage. The proteoglycans consist of a protein backbone and a lot of glycan sidechains attached by a specific xylose-serine link. In normal cartilage these glycans are chondroitin-sulphate and chon-trioitin-6 sulphate, with an increasing contribution by keratan sulphate as we grow older. The hugely coiled molecules keep out, by steric hindrance, other large molecules and yet are held in place by the collagen framework. You cannot, for instance, press them out. Linn and Sokoloff with 1000 lb (454 kg) pressure squeezed out some drops of tissue fluid with 0.2 g/100 ml (2 g/l) protein only. And yet when this protein backbone of cartilage is attacked by papain, as shown by Lew Thomas in New York a long time ago, or by substances releasing lysosomal enzymes as shown by the Cambridge Group, and the molecules are broken up, the cartilage loses its metachromasia and rabbit ears flop due to loss of chondroitin sulphate into the bloodstream; the floppiness lasts until enough proteoglycan has been resynthesized. Thus the stiffness of the disc depends on the proteoglycan and its coherence on the collagen fibres.

Besides cartilage other tissue components of the spine include ligaments, both elastic like the ligamentum flava, and collagenous, both of which may calcify.

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and ossify, and bone. Bone is built of the same components as cartilage plus hydroxyapatite crystals, the latter developing first, as Clark Anderson has shown, in the matrix vesicles. All these tissues contain collagen fibrils, proteoglycans, structural glycoprotein, and sometimes elastin, and our knowledge of them has increased enormously in the last 30–40 years, due to pioneers like Karl Meyer, who initially in 1938 fired my enthusiasm in this field, Jerry Gross, Mathews, Al Dorfman and others too numerous to mention, and in England, Crick, Astbury, Helen Muir, Partridge, Harkness, among many others. But although potentially useful in understanding rheumatic diseases, this new knowledge of connective tissue has contributed in major measure so far chiefly to the understanding of genetic disease, and it is a moot point whether the biochemist has helped the geneticist more or the geneticist the biochemist. The various mucopolysaccharidoses or proteoglycanoses, for instance, have been characterised, like Hurler’s or Hunter’s syndrome with dwarfism and spinal deformity, as due to the accumulation of dermatan sulphate (formerly chondroitin B sulphate) in tissues such as cartilage and internal organs such as aorta, stiff with apparent chondrocytes. Due usually to absence of a degrading enzyme, these genetic illnesses may sometimes give rise to undue laxity of the spine or as in the classical metabolic disease, alkaptonuria, described well by Garrod in 1909, undue stiffness of the spine. It is well known now that, due to lack of homogentisic acid oxidase, homogentisic acid, instead of being broken down to fumaric and acetoacetic acid, accumulates in the body and is excreted in the urine. A polymer is gradually deposited in cartilage and other glycan-containing tissues, rendering them very brittle. The cartilage thus disintegrates under stress, leading to collapse and protrusion of black disc material with often complete loss of disc cartilage, and, as we showed in 1970, the deposition of hydroxyapatite in the discs, giving rise to a very characteristic x-ray, and an interesting ultrastructure with electron-dense material between the collagen fibres.

A rather different calcification of the spine is seen in idiopathic haemochromatosis, a genetically determined error of iron absorption, where calcium pyrophosphate dihydrate is deposited in the annulus fibrosus and ligamentum flavum without greatly affecting its mobility. This seems to be due to iron deviation of pyrophosphates, and we have seen similar pyrophosphate deposition in rheumatoid arthritis synovial membrane, where iron also accumulates as a result of trauma and bleeding. A similar pyrophosphate deposit is seen in an acquired neoplastic disease, hyperparathyroidism, but the major skeletal disabilities here are due to bone fragility and multiple microfractures.

The opposite effect, e.g., of spinal hypermobility, is seen in Ehlers-Danlos syndrome, possibly due to defects in collagen crosslinkage, in Marfan’s syndrome, hyperlysinemia, and homocystinuria, but also in a number of ill-determined familial hypermobility syndromes, and occurring with undue frequency in certain races. Perhaps hence the apparent pre-eminence of Egyptians in belly dancing.

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These genetic diseases I have mentioned are all rare, and since the time of Garrod the basic principles are well known and the mechanisms gradually elucidated. A lot of detail remains to be filled in, and this is now being rapidly supplemented by new cell-engineering approaches. The majority of spinal diseases, however, are far more complicated, and so far molecular biology has prepared an excellent groundwork for their exploitation but has contributed little or nothing yet to their elucidation. They are problem diseases: not involving primary molecular configurations or enzyme defects, but much more sophisticated relationships between aggregates and membranes, often involving the body’s defence mechanisms. Most systemic diseases affecting the spinal cartilages make the back stiffer, and often ultimately more bony, but this same result is achieved by many different mechanisms. The end result looks very much the same but the processes involved are different.

In general they can be classified as metabolic or inflammatory and I want to suggest (without having any real proof) that the metabolic diseases of cartilage that we have already discussed are associated with the excluded-volume effect and that the systemic inflammatory diseases of cartilage may be related to its antigenicity or to the antigenicity of included material. As a corollary one might coin the hypothesis that the inflammatory diseases occur at the reactive periphery of cartilage and that the metabolic manifestations occur in the middle of it—one active and one passive.

The commonest disaster to occur in our backbone is acute prolapse of a disc. The rigidity which results is due to reflex muscle contraction, and despite much current research, epidemiological and biochemical, there is still no reasonable theory to account for prolapse except the retrospectively based diagnosis of ‘inherent local weakness of the annulus’. Such prolapses often occur in the second or third decade.
and bear little relation to the changes which develop with age. Although a good deal of work has been done on the age changes in discs both in man and animals, we know only that the water content is less and the glycosaminoglycan also less, with relative increase of keratan sulphate over chondroitin sulphate. The aging disc seems to be more subject to internal disruption, and this leads to instability and osteophytosis due to periosteal overgrowth. Osteoarthritis itself seldom gives rise to symptoms except in the neck, where it affects the oncovertebral and apophyseal joints, and thereby the cervical roots.

Another frequent but less recognised cause of reflex rigidity and neck pain is interspinous bursitis. Well recognised in the lumbar region (known as Baastrup's syndrome, christened 'kissing spines' by the permissive society), it has also been described clinically in the neck by Michotte—'necking spines' you might say. These bursae are additional to the 158 normal bursae I recorded in the body in 1965 and occur in adult normal spines. The bursae may also be affected in rheumatoid arthritis. In the lumbar spine radiological changes are well recognised, and, pathologically, bursa formation may lead to erosion of bone. The pain is worse on extension and may be severe enough to need excision of the spinous process.

Another common but still mysterious cause of a rigid poker back is similar in many ways to osteophytosis but occurs without disc degeneration, and often without clinical symptoms. This is hyperostotic ankylosing spondylarthritis, described fully by Forestier and Rotes-Querol in 1950 and by many before them. It is noninflammatory and does not occur before 40 years of age. Its incidence increases with age in both males and females to 20% of those over 60. It is characterised by bony bridging between fairly normal, youthful looking discs and the ossification spreads down the right anterolateral ligament in front of the thoracic bodies. It is not confined to this area or to the spine and may cause limitation of the hips or knees. We suggested that perhaps excessive growth hormone (or Daughaday's sulphation factor) might be involved, especially in view of the very similar appearance of the spine radiologically and pathologically in some cases of acromegaly, but this has not been found.

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Even further removed from any molecular explanation, or indeed any explanation at all, are the inflammatory disorders of the spine, which have been my main interest over the last 35 years. The most common of these is rheumatoid arthritis, affecting 2% of the population. It is usually described as a chronic peripheral polyarthritis but involves the spine as well, commonly the cervical spine and more rarely thoracic and lumbar areas. This is not surprising, because out of the 195 true diarthrodial joints of the body 95 (about half) belong to the spine (apophyseal, costo-vertebral, and costotransverse, apart from the occasional oncovertebral and interspinous articulations which I have already mentioned.) Nobody has looked at these very carefully except for the common lesions of the neck. The latter are very important clinically, with pain and undue mobility at the atlantoaxial joint, maximal in flexion. This is associated with odontoid erosion causing the peg to press backwards on the cord, particularly in flexion, and sometimes upwards, with resultant spastic paraplegia or interruption and stretching of the arteries to produce signs of basilar insufficiency (Wallenberg's syndrome), with thrombosis and cerebellar infarction. Fortunately the majority of rheumatoid patients with undue neck mobility survive happily for many years, helped by a neck collar, wise warnings, and their native caution. The pathogenesis of the lower cervical lesions in rheumatoid arthritis has been carefully elucidated by Ball and Sharp.16 Oncovertebral joints are invaded by rheumatoid granulation tissue, and this spreads into the cavities of age-degenerated discs, which become replaced by pannus. Natural ankylosis may sometimes occur, but even in severe cases, with subluxation and cord compression, some recovery may be seen after surgical fixation.

We have seen a similar process17 in the thoracic vertebrae. Here the original rheumatoid focus is in the costovertebral joints, which by contiguity involve the intervertebral disc, producing posterolateral lesions spreading forward and inward and ultimately producing ankylosis. Histologically there is rheumatoid destruction of cartilage and erosion of bone, with reactive sclerosis and loss of red marrow. Some discs appearing radiologically sound may show histologically posterior destruction of the disc. We have also seen lesions at lumbar intervertebral sites where pain, sclerosis and loss of disc space indicate discitis, possibly due to rheumatoid pannus.

In young children with juvenile rheumatoid arthritis, however, the oncovertebral joints of the neck are not involved, since they are then only potential spaces developing into pseudojoints only by the time of adolescence or later. Instead, apophyseal joint involvement is common, and in juvenile chronic polyarthritis (or Still's disease as it was often known in the UK) ankylosis is a not infrequent consequence, affecting the apophyseal joints first and only later intervertebral disc. Because each segmental bone moves as a whole, ankylosis in one joint means immobility of the whole of that segment—contralateral apophyseal joint and intervertebral disc as
well, and sometimes the cervical spine becomes a single solid mass. Another consequence of immobility in children is an increased height/diameter ratio of the vertebrae. A similar effect can occur in adults by a different process (remodelling). Furthermore if ankylosis sets in early, fusion of the ring epiphysis occurs, with permanently miniature vertebrae in each dimension. Thus in childhood fusion and rigidity predominate. In the 14 cases we have examined postmortem fusion of the 2nd and 3rd cervical vertebrae was by far the commonest lesion and this is seen also in adult-onset Still's disease (seronegative polyarthritis and rash). Only when the child becomes adult do we see the occasional adult-type lesions of increased mobility due to subluxation at both apophyseal and disc areas in lower segments.

The original ‘poker back’ historically, however, was ankylosing spondylitis—Marie-Strumpel-Bechteref disease, or what was called in the USA for a long time ‘rheumatoid spondylitis’. Everyone is now agreed that ankylosing spondylitis is a completely different disease from rheumatoid arthritis, on the following grounds: predilection for young males, familial distribution and B27 association, cartilaginous joint lesions, pubic and manubriosternal lesions, disc lesions, acute uveitis, and absence of IgM rheumatoid factor. What, however, is its nature? It is one of the more familial of the rheumatic diseases and related genetically in some families also to ulcerative colitis and psoriasis. A peculiar spinal lesions may occur in psoriasis with much subperiosteal new bone similar to the characteristic and often extensive periosteal deposits elsewhere. Our new knowledge of the association of spondylitis with B27 tissue antigen ties in very well with the increased incidence of both this HLA Ag and ankylosing spondylitis in the Haida Indian and other populations compared with Caucasians (one of the few differences brought out by epidemiological studies in this field).

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Usually genetically determined disease implies biochemical faults, and particularly enzyme defects and the similarity of the spinal changes in ankylosing spondylitis to those of hypophosphataemia, or fluorosis, with its ossified ligaments, might lead people to regard ankylosing spondylitis also as a primary metabolic disorder. Van Swaay has postulated abnormal calcification of cartilage as the primary step in the genesis of syndesmophytes. My own studies of spinal material from 17 out of 24 necropsied cases of ankylosing spondylitis led me to postulate in 1968 an inflammatory mechanism, and this has in general been confirmed by Ball, who described the disease as essentially an enthesopathy, or a lesion of ligamentous insertions. While I agree that these occur, I have also seen them in rheumatoid arthritis, and I think that the essential lesion in ankylosing spondylitis is a direct inflammatory vascular reaction to some component of cartilage, whether this is at a ligamentous insertion or at an intrusion of bone, blood vessels, or into calcified fibro- or hyaline cartilage.

It is not enough to define a disease in terms of where it occurs (and we would also have to expand ‘tendon insertions’ to include such various tissues as the iris, the aorta, the synovial membrane and the discs) but only of how it occurs, and this we have not yet reached. In contrast to 58 published necropsy cases a few of our cases were comparatively early deaths from amyloid within 5–10 years of onset. The sacroiliac joints in such cases showed marked inflammatory lesions with lymphocytes, plasma cells, and chondroclasts: similar lesions were seen in the disc margins. Limitation here was reflex, due to pain, and x-rays were negative. Later bone begins to replace the scar tissue, but it does not at this stage involve unscarred, uneroded discs. Even in long-standing cases with bambooing, active inflammatory erosion of cartilage can still be seen beneath the bony bridge. The so-called ‘Romanus lesion’ seen on the x-ray (which leads to squaring from bone erosion) is due to reactive bone sclerosis in an inflamed but still moveable segment, often the only such segment still mobile. Its histology is essentially the same as before and the same as that of the discitis seen radiologically and grossly. Immobilisation of the segment leads to ossification and healing. If this is an immunological reaction to some included antigen, the latter must sometimes involve aortic or iris tissue, since these organs are affected in 1% and 30% respectively.

Relapsing polychondritis with collapse of ears, larynx, and nose is a very similar disease affecting cartilage throughout the body, and like ankylosing spondylitis also involves the eyes with scleritis, the aorta with pulseless syndrome, with peripheral arthritis, and with lesions of the intervertebral discs, similar to the discitis of ankylosing spondylitis. We have found circulating antibody to human cartilage by immunofluorescence in one out of 5 cases, and cell mediated immunity to chondromucoprotein (kindly supplied by Dr Helen Muir) by the macrophage inhibition test using guinea-pig macrophages in 4 out of 5 cases. These are similar results to those Herman et al. Thus this appears to be another type of autoimmune disease. But so far, despite the similarities, we have failed to find either type of immunological reaction in ankylosing spondylitis, although humoral anticollagen antibody may be seen in rheumatoid arthritis. Such studies should be
repeated using cartilage from spondylitis as antigen. The use of normal tissue may be quite irrelevant and we should be looking for bacterial and other incorporated residues.

Thus, by combining the neglected area of anatomical study with the noisy and crowded area of immunology, both based firmly on the new knowledge of molecular biology, it may prove possible soon to sort out some of these mysterious diseases.

In summary, we know little yet about the stiffening which results from disease of this rigid but bendable tube. Translating into the larger sphere, when the wind of change blows, it is a great deal better to bend than to break. Rigidity, however, is neither an age-related phenomenon nor a disease but a symptom of disease. We have to search to find its cause. At the same time we have to recognise that survival for mankind depends also to some extent on stability as well as mobility. We have to be both stiff and bendable, and the healthy vertebrate spine is not a bad example to emulate.

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References

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