A consensus

Diseases of connective tissue: a consensus

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The accelerated rate of acquisition of new chemical, biological, physical, and mechanical knowledge of the connective tissues may obscure pathological aspects of connective tissue diseases rather than clarify their nature. To guard against this possibility periodic, critical reviews of analytical and experimental advances are salutary. They provide an opportunity not only to assess recent investigations but also to compare the widely differing problems encountered in connective tissue diseases in different parts of the world. They also offer an opportunity to reclassify connective tissue disease in the light of new understanding.

Summary of new knowledge

Much of our information relates to the biology, biochemistry, physics, and mechanics of the connective tissues; much less concerns the precise manner in which these tissues are injured or disturbed in the wide range of disorders included in this review. The fibroblast (see M. Abercrombie (Abercrombie, 1978) at page 1)—ubiquitous, resilient, and versatile—is the prototype on which much of our present understanding of connective tissue pathology is based. Identified in tissue culture partly by shape, partly by spatial relationships to other cells, the cell is contractile and motile. Much of its resources is devoted to producing the contractile proteins that permit the active, slow directional movement that ceases when cell-to-cell contact inhibits movement. Ready multiplication depends on cell density and on the local concentration of components in the culture medium. However, the limitation of replicative cycles to 60 or so, the Hayflick effect, may be an artefact of culture caused by the elimination of a class of stem cells able to perpetuate multiplication indefinitely *in vivo*.

An essential function of the fibroblast, and one central to our understanding of the diseases of connective tissue, is the manufacture and export of structural and enzymic proteins, of collagen and elastin, and of the proteoglycans. It is in the proportion of energy given to producing the pro-

teoglycans that chondrocytes (see R. A. Stockwell (Stockwell, 1978) at page 7) differ most obviously from fibroblasts. Chondrocytes synthesise and export much collagen and sometimes elastic material; but the cytological recognition of chondrocyte-rich tissues such as hyaline articular cartilage is most readily affected by identifying the abundant, proteoglycan-containing matrix. Thus a chondrocyte can be said to be a connective tissue cell in which the formation of a proteoglycan-rich matrix dominates all other activities. Although this over-simplification can be misleading, it gives an important guide to the manner in which diseases of chondrocytes such as chondrodystrophia fetalis, the chondrodystrophies, and the neoplasms of cartilaginous tissues are manifested clinically.

Honor Fell (Fell, 1978; see page 14) reminds us of the distinctive properties of synoviocytes. For pathologists the two most interesting characteristics of synoviocytes are their voracious capacity for phagocytosis and their preoccupation with the synthesis of hyaluronic acid. However, pathologists often remark on the neoplasm-like proliferation of these cells and note that metastatic carcinomatosis of the synovial tissue is curiously rare (or seldom recognised).

Contractility could be said to be a fundamental property of all cells. It is not a feature of the hyaline cartilaginous chondrocyte, trapped like a crustacean in a chondroitin sulphate-rich gel of its own origin, but the same cells may move in monolayer culture when freed from this constraint and from contact inhibition. Nevertheless, it is in the muscle cell (see J. C. Sloper, M. C. Barrett, and T. A. Partridge (Sloper *et al.*, 1978) at page 25) that we find contractility refined to its biological limit to provide locomotion in the multi-cellular parent organism, and diseases of muscle most often appear as disturbances of contractility.

The principal exports of the connective tissue cells are collagen (see D. S. Jackson (Jackson, 1978) at page 44, and A. J. Bailey (Bailey, 1978) at page 49) elastin (Bailey, 1978) (and presumably elastic microfibrillar glycoprotein), and the proteoglycans (see

H. Muir (Muir, 1978) at page 67). To the pathologist the advances in understanding of the mechanisms of synthesis, export, maturation, and metabolism of these materials are crucial: the new knowledge permits logical identification and classification of disease and the sensible and purposeful planning of experiments undertaken to examine pathogenesis and natural history. This logic has led Lapière and Nussgens (1976) and Levene (see C. I. Levene (Levene, 1978a) at page 82) to the reclassification of many of the connective tissue diseases on the basis of inherited or environmental disorders of collagen production and maturation (see F. M. Pope and A. C. Nicholls (Pope and Nicholls, 1978) at page 95). Similarly, the systematic identification of enzymic defects in the inherited mucopolysaccharidoses (McKusick, 1972), the glycosaminoglycan-storage diseases, has promoted rational classification of these uncommon disorders. In turn, this has led to important success in correcting inherited deficiencies by the transplantation of fibroblasts to children born with deficiencies of the enzymes needed for normal glycosaminoglycan degradation (see M. F. Dean (Dean, 1978) at page 120). Compared with the extent to which understanding of collagen and, to a lesser extent, elastin has advanced progress in unravelling the problems of the basal lamina (basement membrane) has been limited (see J. T. Ireland (Ireland, 1978) at page 59). However, the presence in basal laminae of type IV collagen (Kefalides, 1974) and an appreciation of the role of the basal laminae in controlling processes such as glomerular capillary filtration suggest that within the next decade the detailed composition and physiological role of this structure will be better understood, to the great benefit of pathologists. Thus the selective identification of type IV collagen in tissue sections by the histochemical method of Böck (1978), a technique based on the relatively high cystine content of type IV collagen (8 half-cystine residues/1000) compared with type III (2 half-cystine residues/1000) and types I and II (from which cystine is absent), suggests that understanding of basal laminar disease may advance quickly.

Advances in enzymology in relation to the pathogenesis of connective tissue disease have not been limited to analyses of lysosomal function (see L. Bitensky (Bitensky, 1978) at page 105), although it could fairly be claimed that the lysosomal concept (de Duve *et al.*, 1955) was the spark that ignited the present explosive advance in knowledge of the cathepsins in inflammation (Dingle, 1969) and, in particular, of the neutral collagenases in rheumatoid arthritis (Woolley *et al.*, 1977, 1978). Concurrently, the genetic basis for such common forms of polyarthritis as rheumatoid arthritis and ankylosing

spondylitis and the evidence implicating the HLA antigens in the origin of these diseases (Brewerton *et al.*, 1973; see D. A. Brewerton (Brewerton, 1978) at page 117) have been under intensive study in experiments that move more and more towards an indictment of microbiological agents such as *Klebsiella pneumoniae* as initiating factors (Ebringer *et al.*, 1978). However, there is not yet any conclusive evidence that rheumatoid arthritis is provoked by any known infective agent, despite striking pointers towards the role of mycoplasmas (Taylor-Robinson and Taylor, 1976), diphtheroids (Duthie *et al.*, 1976), and viruses (Marmion, 1976; Hart and Marmion, 1977). Probably any putative infective agent would act by indirect, immunological mechanisms to cause and perpetuate tissue injury. A. M. Denman (Denman, 1978; see page 132) advances good circumstantial evidence to show that at least five such mechanisms are possible. Very good reasons exist for suggesting that a C-type RNA virus operates in the case of systemic lupus erythematosus, at least in the heritable dog model of the disorder (Lewis and Schwartz, 1976). That such an antigen can act globally to alter or impair the immunological mechanism—leading to the production of many abnormal antibodies, often of autoimmune character (see E. J. Holborow (Holborow, 1978) at page 144)—seems beyond dispute. It remains of crucial importance to obtain evidence of a similar or analogous mechanism in rheumatoid arthritis, and there is some reason to believe that this evidence is forthcoming (Panayi, 1976).

Recent discussions (Jayson, 1977) emphasise our better appreciation of the nature of the process of fibrosis, so important in determining the clinical behaviour and natural history of synovitis in rheumatoid arthritis; of cardiac valve disease in rheumatic fever; of oesophageal, cardiac, and dermal disorders in systemic sclerosis; and of the destructive and occlusive lesions in hepatic fibrosis (see J. O'D. McGee and A. Fallon (McGee and Fallon, 1978) at page 150) and atherosclerosis (see C. I. Levene (Levene, 1978b) at page 165). The origins of the lung lesions in the pneumoconioses (see P. C. Elmes and J. C. Wagner (Elmes and Wagner, 1978) at page 158) and the characteristic pulmonary changes that develop in response to a wide variety of lung-injuring chemicals, physical agents, dusts, aerosols, and foreign antigens have suggested ways in which the connective tissues can be injured. Similarly, the demonstration (McGee and Fallon, 1978) that excess collagen formation in hepatic fibrosis can result from proline hydroxylase activity emphasises how analogous changes may explain the chronic inflammation and the fibrosis of rheumatoid synovitis, ankylosing spondylitis (see

J. Ball (Ball, 1978) at page 200), and other inflammatory disorders of the connective tissues.

In the case of osteoarthritis (see S. Y. Ali (Ali, 1978) at page 191) argument still rages on the nature of the first alteration in joint function and in hyaline articular cartilage structure and composition that may precede the clinical disease (Gardner *et al.*, 1978). It is certainly possible (Ali, 1978) that altered calcium hydroxyapatite metabolism can promote cartilage injury; the analogy with the accumulation in cartilage of the calcium pyrophosphate of chondrocalcinosis is very close (see P. Dieppe (Dieppe, 1978) at page 214). However, it seems to many that the progressive lesions of selected areas of hyaline cartilage are distinct from the non-progressive alterations that deform hip joints examined at necropsy (Byers *et al.*, 1970). It certainly seems difficult to account for focal lesions by a metabolic mechanism that could be held to predispose to generalised calcium hydroxyapatite deposition in load-bearing cartilage. Comparable difficulties attend our present views on gout (see J. T. Scott (Scott, 1978) at page 205). Here the problem is to account for the selective deposition of urate in only very limited connective tissue sites in the face of high plasma concentrations of urate that raise the extracellular fluid urate concentration in almost all parts of the body.

Behind these metabolic changes, probably independent of, although associated with, altered immunological responsiveness, lie the connective tissue phenomena that we attribute to ageing (Schofield and Weightman, 1978). Distinct from connective tissue alterations in growth and maturation, age changes are now believed to be subtle, widespread, and multifactorial. In some circumstances altered immunological reactivity and age may both contribute to the accumulation of the AA protein of amyloidosis, an accumulation that reminds us of the genetic background of some rare forms of this curious disorder (see J. R. Hobbs (Hobbs, 1978) at page 128). However, to attribute to the molecular anomalies of ageing any particular connective tissue disease such as osteoarthritis or intervertebral disc disorder (Ball, 1978) remains as much beyond our present state of understanding as does the explanation of most cases of amyloidosis.

Ignorance of the connective tissue diseases

The imaginative *Encyclopedia of Ignorance* (1977) could well be extended to include a chapter on the diseases of connective tissue. In this encyclopaedia each authority writes on aspects of science, defining what is not known, not what is. What do we not know of the diseases of connective tissue?

It is hardly possible to consider a single disease of the connective tissue system without immediately realising the great gaps in our understanding. For example, advances in the therapy and prophylaxis of gout have been so spectacular that we are inclined to overlook our ignorance of the ways in which selected connective tissue foci come to act as niduses for aggregates of monosodium urate dihydrate crystals (Scott, 1978). The discovery of an association between the HLA antigens and diseases such as ankylosing spondylitis only emphasises the fact that we are still wholly ignorant of the ways in which selected connective tissues such as the synovial and fibrocartilagenous joints, and the entheses, become sites for sustained inflammation. The role of microbiological agents in provoking focal inflammation via hypersensitivity mechanisms is suspected but wholly unproved. The reasons why the aortic valve and the uveal tract are implicated are entirely obscure. In much the same way, progress in unravelling the pathogenesis of osteoarthritis has failed to keep pace with dramatic advances in the techniques of arthroplasty. It remains probable that the term primary osteoarthritis conceals the existence of a cluster of disorders, all terminating with similar clinical signs and symptoms.

In this account I have chosen to review some unanswered questions that relate respectively to osteoarthritis, rheumatoid arthritis, and the connective tissue neoplasms. Firstly (in relation to osteoarthritis), do we properly understand the surface structure of articular cartilage? Secondly (in relation to rheumatoid arthritis), do we have a proper model with which to undertake experimental laboratory studies? Thirdly (in relation to primary and metastatic neoplasms of the synovia), is there a proper appreciation of the neoplastic diseases of connective tissue and of the apparent immunity of the synovial tissues to neoplasia?

WHAT IS THE TRUE NATURE OF HYALINE ARTICULAR CARTILAGE SURFACES?

An articulating Cartilage is an elastic Substance uniformly compact, of a white Colour, and somewhat diaphanous, having a smooth polished Surface covered with a Membrane; harder and more brittle than a Ligament, softer and more pliable than a bone (William Hunter, 1743).

Analytical microscopy of hyaline articular cartilage surfaces is dominated by the salutary chemical observation that cartilage is a highly hydrated, fibre-reinforced gel in which resistance to tensile stress is largely a property of type II collagen and resistance to compressive stress a property of the proteoglycans (Elliott and Gardner, 1978), their

aggregates, and the associated water. Mature hyaline cartilage is avascular and aneural. Although chondrocytes respire at relatively low O_2 tensions the loss during histological preparation of the normal articular arterial blood supply, exposure to abnormally low O_2 tension, dehydration, and protein denaturation (fixation) must all, by definition, alter and distort the very chemical and physical attributes that determine the uniqueness of cartilage as a biological material.

Momentary thought will remind the observer that synovial joints do not have 'spaces' or cavities *in vivo*. Articulations form *in utero* when physical and chemical changes in the mesenchyme lying

between the bone rudiments of the embryonic limb alter the properties and appearance of the connective tissue matrix so that it becomes fluid. There is no 'space'. The articulation is a continuum in which movement is permitted in the fluid centre of a bone-hyaline cartilage-synovial fluid-hyaline cartilage-bone structure.

The articular cartilage surface seen in the living human synovial joint in the surgical operating theatre is apparently smooth. Light is reflected brightly from the anatomical cartilage contours and there is no sign of detailed irregularity. This is the appearance recognised by William Hunter (1742-43), by Barnett *et al.* (1961), and by Davies (1969). However, as

a

Fig. 1(a), (b) Photomicrographs of surface of fresh, unstained, and unfixed hyaline human articular cartilage from lateral condyle of knee of 13-year-old girl. Pale ovoid features at top left corners and left centres are fluid droplets ($\times 150$).

(a) Cartilage viewed in incident white light under conventional light microscopic conditions. (b) Same field viewed with incident green light, wavelength 550 nm, under interference conditions. Closeness of contour lines indicates the steepness of slope of a feature. Marker lines indicate 100- μ m distance (reproduced by courtesy of Dr R. B. Longmore).

b

McCutchen (1978) points out, Davies *et al.* (1962) detected surface waviness no higher than 500 Å over lengths of 5 µm and 0.2 µm over distances of 10 µm, but stated the surfaces were 'smooth'. Yet a 0.2 µm pit 10 µm in diameter has sides that slope at more than 2°.

Not surprisingly, therefore, incident light (Gardner and McGillivray, 1971a, b) and scanning electron microscopy (SEM) (McCall, 1968; Gardner and Woodward, 1968, 1969; Inoue *et al.*, 1969; Walker *et al.*, 1969) showed that adult and embryo mammalian and avian articular cartilage surfaces, apparently smooth when seen first at disarticulation, are delicately irregular and detectably rough when examined moist or dry in the unloaded, *in-vitro* condition (Fig. 1).

The surface is shaped grossly by anatomical contours. A hand lens reveals that the contours bear 0.4–0.5 mm irregularities. A stereoscopic dissecting or incident light microscope then displays a fine pattern of haphazardly disposed tertiary hollows and undulations. The pattern is neither orderly nor readily explicable in anatomical terms. Even with acutely angled incident light arranged to accentuate shadow and contour the detailed structure of the surface hollows is not easily seen; much of the incident light passes into or through the cartilage, outlining the component chondrocytes.

When the arterial supply to the limb is cut off by a clamp or tourniquet the appearances of the exposed hyaline cartilage quickly change. Drying accelerates; the 'highlights' that result from the reflection of incident light from the surface disappear; and small, pale, circumscribed zones of pallor suddenly emerge, each the diameter of a surface undulation or of an underlying chondrocyte.

Debate still continues vigorously on the nature of the surface tertiary irregularities and on whether they are caused or influenced by artefact (Clarke, 1973; Ghadially *et al.*, 1976; Ghadially, 1978). It is certain that the tertiary surface undulations are invariably present on fresh unfixed, unloaded, mammalian hyaline articular cartilage examined under conditions that obviate drying (but in the absence of a direct articular blood supply). In these circumstances the 20–40 µm diameter undulations can be measured by reflected light interference microscopy (Longmore and Gardner, 1978) and their height, diameter, and frequency shown to change with age (Longmore and Gardner, 1975). It is equally certain that fine, ridge-like artefacts, seen by SEM, can be introduced at joint surface margins by compression or distortion (Ghadially *et al.*, 1976). However, the artefactual ridges can be avoided by adopting 'optimal' preparative techniques (Cameron *et al.*, 1976).

High resolution SEM suggests that the articular surface is formed of interlacing collagen bundles. Preparation for SEM normally necessitates fixing and dehydrating the material before it is exposed to the electron beam under conditions of high vacuum. Virtually all water is removed; the proteoglycans are inevitably displaced on to the resilient superficial collagen bundles as water is lost. Presumably because of this displacement the presence of the very large proteoglycan molecules is not easily confirmed by SEM.

When the same surfaces are examined by transmission electron microscopy (TEM) in thin, perpendicular sections of well-prepared material, such as the baboon femoral condyles we have examined recently, the articular surface is shown to be formed not of mature collagen bundles with conspicuous cross-striations but of a lamina of uncertain composition about 60 nm thick. This is the layer depicted, described, and analysed by Balazs *et al.* (1966) and shown by other authors including Bjelle and Sundström (1975). The observations of Balazs *et al.* were on cattle material, those of Bjelle and Sundström on human. The weight-bearing surface is therefore not the misleadingly conspicuous collagen mat seen by SEM but a very thin, delicate, ultra-microscopic lamina—perhaps hyaluronate (Balazs *et al.*, 1966), perhaps glycoprotein—enmeshed (Fig. 2) with the most superficial collagen bundles on its deeper aspects and in molecular continuity with the hyaluronate-protein of the synovial fluid on its superficial aspect. Preliminary observations also reveal the presence of this lamina on the femoral condylar surfaces of rat hyaline cartilage. Perhaps a finite term, lamina obscurans, should be used to describe this 60-nm layer to emphasise its distinction from the 2–10-µm lamina splendens of MacConnail identified by light microscopy.

There are indications, therefore, that our knowledge of hyaline articular cartilagenous surfaces is incomplete. The high water content of hyaline cartilage and the ease with which the surface structure can be distorted mean that any experiment in which drying is permitted or encouraged is bound to introduce severe artefact. This can be avoided to a considerable extent by observing and measuring freshly excised cartilage by techniques such as reflected light interference microscopy that permit moist material to be analysed untouched. But the limit of optical resolution by this method is $\pm \frac{1}{4}$ wavelength of the monochromatic light chosen for analysis. Inevitably the next approach to the surface of load-bearing cartilage must be with low-temperature analytical methods that allow the techniques of high resolution SEM and TEM to be applied to fresh cartilage held at low temperature with

Fig. 2 Surface lamina obscurans of lateral femoral condylar cartilage of baboon. At top: stellate arrays of electron-dense material, presumably synovial fluid hyaluronate-protein. At centre: lamina obscurans, mainly featureless with no apparent collagenous or proteoglycan structure, merging with (at bottom) surface layer of large collagen fibres that extend deeply to comprise the lamina splendens. (Epon-embedded material, uranyl acetate, lead citrate stained $\times 112\,000$)

collagen, proteoglycan, and water in their normal *in-vivo* spatial relationships. We may state this proposition in another way: except for the single, preliminary photograph published by Cameron *et al.* (1976) no one has yet seen or photographed at high resolution intact, normal articular hyaline cartilage surfaces in the fully hydrated state. Judged from progress in understanding cartilage surfaces in perpendicular section, the results may be surprising.

IS THERE AN ANIMAL MODEL OF RHEUMATOID ARTHRITIS?

A model, in the sense in which this word has come to be used apropos of scientific investigation, is a symbol that is being used as an instrument (Arnold Toynbee, 1972).

It is almost always valuable to examine a model to elucidate the natural history of a disease. But it is not necessary to choose a model that exactly replicates each feature of the disease under investigation. A model serves to throw light on aspects of the disease, clarifying pathogenesis rather than exactly reduplicating it. 'Models' of rheumatoid arthritis are therefore often analogues not replicas. With this in mind, the observation that there is no exact replica in any animal species of rheumatoid arthritis is of great interest but it does not prevent valuable experiments with analogues from proceeding. To illustrate the manner in which recent investigations have thrown light on rheumatoid polyarthritis without entirely explaining its nature and origin we may reasonably consider (1) anti-

collagen arthritis (Trentham *et al.*, 1977, 1978) and (2) immune complex synovitis (Poole and Coombs, 1977; Poole *et al.*, 1978).

Anticollagen arthritis

It has been known since 1954 that local intradermal injection into the skin of rats, but not of other mammals, of small but finite quantities of finely ground, heat-killed mycobacteria suspended evenly in mineral oil (Freund's complete adjuvant (CFA)) produces a delayed polyarthritis of characteristic pattern 9 to 17 days later. The arthritis is not a replica of rheumatoid arthritis but is a valuable model with which to study aspects of inflamed joints. The presence of homologous tissue antigens—for example, synovia or skeletal muscle—is not necessary for the response to occur and does not determine organ specificity of response, and incomplete adjuvant (ICFA) is ineffective.

Trentham *et al.* (1977) showed that under comparable circumstances human, chick, or rat mature cartilage type II collagen, given in complete or incomplete adjuvant, provoked autoimmune arthritis in 41% of 348 injected rats. Type I and type III collagens did not have this effect in 181 control animals and analogous changes were not produced by the injection of human cartilage proteoglycan. It was also shown that although a control arthritis could be caused by injecting intradermally 0.1 ml CFA containing 10 mg *Mycobacterium tuberculosis*/ml the CFA adjuvant used for all collagen immunisations, containing 0.5 mg *Mycobacterium butyricum*/ml, did not cause adjuvant arthritis in 30 control animals. Native type II collagen modified by limited pepsin digestion still caused arthritis, suggesting that type-specific determinants in the helical region of the collagen molecule were responsible for the disease, and $\alpha 1$ (II) chains were not arthritogenic.

The experimental type II collagen arthritis is apparently the only model of arthritis in which disease can be regularly induced with incomplete adjuvant together with homologous tissue injected intradermally. The suggestion has been made that this is an unusual property attributable to type II collagen. The resultant arthritis is similar to, but not identical with, the polyarthritis following adjuvant alone. Among the differences are that anticollagen arthritis is more often monarticular, does not extend, and is not accompanied by mucosal lesions. In our experience, adjuvant arthritis can be regularly caused in more than 90% of rats injected with CFA. The frequency of the response in anticollagen arthritis is clearly lower. Since the presence of both the triple helix of type II collagen and an oil, as incomplete adjuvant, are both essential for the development of anticollagen arthritis there is

speculation about the nature of the collagen/adjuvant relationship. The explanation does not appear to be attributable to the persistence of small quantities of proteoglycan in the collagen preparations, although the presence of peptidoglycans in bacterial preparations used in complete adjuvants suggests this possibility.

Evidently, therefore, a new model of experimental arthritis of exceptional interest has been devised. Already Trentham and his colleagues (Trentham *et al.*, 1978) have extended their analysis of the immunological aspects of their model, showing that the type II collagen triple helix has unique cellular and humoral immunogenic characteristics as well as being most unusually arthritogenic. Obviously this immunogenic capacity may be invoked indirectly to explain the persistence of inflammatory cartilage injury in a variety of human and animal disorders. It is not so easy to understand why the responsible anticollagen response should injure the margin of the hyaline articular cartilage of rat knee joints while leaving intact the hyaline cartilage of structures such as the trachea. However, increasing evidence of collagen polymorphism could be one explanation for the selectivity of anticollagen tissue injury, and no doubt this suggestion will shortly be examined.

Immune complex synovitis

The onset of adjuvant arthritis and of collagen arthritis is marked by an acute, exudative inflammatory reaction. In the former polymorphs are numerous, in the latter mononuclear cells exert an early predominance. Except in these early lesions neither response resembles rheumatoid polyarthritis in man particularly closely. Indeed, in some respects, including the rapidly progressive osteoclastic bone destruction with exuberant new bone formation, the analogy between adjuvant arthritis and human disease recalls the microscopic changes of granulomatous disorders such as leprosy rather than the less destructive, chronic non-specific inflammation of rheumatoid arthritis. But the interest of these experimental animal disorders to students of rheumatoid arthritis lies not in the reduplication of the characteristic histological features of this disease but in the way in which they show how, in principle, tissue-damaging mechanisms can follow immunological injury.

I therefore argue that the identification in experimental animal arthritis models of tissue lesions with those of human rheumatoid arthritis is neither to be anticipated nor expected. There is no *exact* animal model of rheumatoid arthritis. We know of no animal in which small finger and toe joints become inflamed in early- to middle-aged females and in

which systemic disturbances—including anaemia, fever, altered plasma protein levels, and a remitting, polyarticular joint disease—progress over half a life time to fibrous ankylosis, accompanied, quite commonly, by systemic lesions and followed, in one-fifth of instances, by inexorable amyloidosis. There is no known animal replica of this state. However, this need not occasion surprise: if the hypothetical agent causing rheumatoid arthritis could be isolated and administered by an appropriate route to, say, a rhesus monkey or a dog there is every reason to expect a response that is species specific and characteristically different from that in man.

Consequently those authors who, because they have caused microscopic changes in the synovial joints of an animal that closely resemble those in the human condition, imply that they have *directly* advanced understanding of the pathogenesis of human rheumatoid arthritis do not represent the point of their experiments completely.

Among many recent papers in which this argument is implicit, if not explicit, are the recent reports of Poole and Coombs (1977) and of Poole *et al.* (1978). The title of both papers includes the phrase 'rheumatoid-like' in relation to the investigation of the synovial changes that develop in rabbits when challenged with foreign protein in such a way that a response of 'serum-sickness' type ensues. But the importance of these reports does not lie in the closeness with which the joint lesions recall those of the early human disease. The human lesions, after all, are characteristic but not in themselves pathognomonic (Gardner, 1972). The reports are of value because for the first time they properly describe this form of immune complex synovitis in microscopic detail. It is valuable to be reminded (Poole and Coombs, 1977) that although experimental 'serum sickness' polyarthritis was clearly documented by Klinge (1929) and mentioned by Hawn and Janeway (1947) neither investigator provided detailed microscopic descriptions of the consequent tissue changes. But it is irrelevant to our understanding of human rheumatoid arthritis to extend the proposition by suggesting that the rabbit model replicates the human disease histologically: the model is a Toynbee analogue, not a replica.

WHAT IS THE NATURE OF CONNECTIVE TISSUE NEOPLASIA?

Cancer is a biological phenomenon whose elucidation is bound up with advances in a number of key fields of present day biology. There is no single cause (Julian Huxley, 1958).

We know practically nothing of the causes of the human connective tissue neoplasms. They are many and diverse. The oncology of the synovial (Table 1),

cartilagenous (Table 2), and other soft tissue (Table 3) neoplasms is in its infancy: their study is still in the first, descriptive stage of scientific inquiry. However, advances are being made and the widespread use of transmission electron microscopy (Dische *et al.*, 1978; Winkelmann *et al.*, 1978) is adding to our understanding of the cellular nature of these disorders and improving classification. The analytical aspects of human connective tissue neoplasia have been delayed by the rarity of the lesions in clinical practice and by the difficulty of obtaining fresh material suitable for modern analytical and biological techniques of study. Much more is known of the experimental neoplasms caused in other species.

Are there then clues to the origin of the connective tissue neoplasms in the evidence presented today on cell structure and behaviour? Can we, for example,

Table 1 *Neoplasms of the synovium (after Fechner, 1976)*

Benign	
	Synovioma Haemangioma Lipoma
Malignant	
Primary	Synovial sarcoma Epithelioid sarcoma Clear cell sarcoma Malignant giant cell tumour of tendon sheaths and soft tissue Synovial chondrosarcoma
Metastatic	
Neoplasm-like disorders of synovia	
	Synovial chondromatosis Pigmented villonodular synovitis Intra-articular localised nodular synovitis Extra-articular localised nodular synovitis Ganglion and synovial cyst

Table 2 *Neoplasms of cartilage (Jaffe, 1969)*

Benign	
	Chondroma Osteochondroma Chondromyxoid fibroma Chondroblastoma
Malignant	
	Chondrosarcoma Chondrosarcoma of soft parts Malignant chondroblastoma Chordoma
Neoplasm-like disorders of cartilage	
	Chondroid metaplasia Dyschondroplasia Chondrodystrophies Ectopic cartilage Fracture callus Chondroid material of 'mixed' tumours and teratomata

Table 3 *Neoplasms of fibrous tissue (fibromas)*
(Enzinger et al., 1969)

Fibromas	Fibroma durum
	Fibroma molle (fibrolipoma)
	Dermatofibroma (histiocytoma, sclerosing haemangioma)
	Elastofibroma (dorsi)
Neoplasm-like disorders of fibrous tissue (fibromatosis)	Cicatrical fibromatosis
	Keloid
	Nodular fasciitis (pseudosarcomatous fibromatosis)
	Irradiation fibromatosis
	Penile fibromatosis (Peyronie's disease)
	Fibromatosis coli
	Palmar fibromatosis
	Juvenile aponeurotic fibroma (calcifying fibroma)
	Plantar fibromatosis
	Nasopharyngeal fibroma (juvenile angiofibroma)
	Abdominal fibromatosis (abdominal desmoid)
	Fibromatosis or aggressive fibromatosis (extra-abdominal desmoid)
	Congenital generalised fibromatosis
	Dermatofibrosarcoma protuberans
	Fibrosarcoma

relate the analysis of the normal chondrocyte to the natural history of chondrocytes in chondroid metaplasia, chondroma, chondroblastoma, chondromyxoid fibroma, and chondrosarcoma and to the growth of ectopic cartilage, to the cartilage of fracture callus in delayed healing, and to the cartilage component of 'mixed' tumours and of the teratomata?

One result of the new investigations outlined in the earlier papers of this symposium will be an upsurge in interest in the biochemistry and cytology of the human connective tissue neoplasms. When a chemical and morphological study has been completed we may hope that, at worst, a new logical classification will be available and, at best, new light will have been thrown on the origin and cellular relationships of these tumours. In preliminary inquiries of this nature we have begun to correlate the microscopy, electron microscopy, and biochemical composition of selected connective tissue neoplasms. For example, a myxoma of the mandible (Fig. 3) in a girl aged 17 years was found to contain

Fig. 3 *Myxoma of mandible (scale = centimetres) of girl aged 17 years. Electron microscopy showed predominance of poorly differentiated myxoid cells. On chemical analysis matrix contained a predominance of hyaluronic acid (reproduced by courtesy of Dr P. S. Hasleton).*

much hyaluronic acid. The neoplastic tissue was identified as 'myxoid' by light and by electron microscopy. In another example, a mesothelioma of pleura of high cellularity contained connective tissue stroma in which collagen and sulphated glycosaminoglycans were the preponderant molecular species. These instances show that almost all the analytical techniques mentioned in this symposium could be brought to bear on the difficult question of the nature of the fibrous, cartilaginous, and synovial neoplasms, encouraging new understanding and classification. Already, cartilaginous neoplasms have been identified that display endocrine functions (Mack *et al.*, 1977).

Can we obtain other clues to the behaviour of the

connective tissue neoplasms from generalisations arising from the present discussion? The analyses made by Abercrombie (1978), Fell (1978), Stockwell (1978), and Sloper *et al.* (1978) have done more than concentrate our minds on current knowledge of some of the most important connective tissue cells. They have given us a new perspective of the outstanding problems in the neoplastic and neoplasmlike disease of the connective tissues. We can begin to relate views on the behaviour of normal cartilage cells to the natural history of the cartilaginous neoplasms and of the teratomata and to extrapolate from the normal synovial cell to the monophasic (Mackenzie, 1977) and biphasic synovial sarcomata (Fig. 4).

Fig. 4 Synovial sarcoma, biphasic. Epithelial cells at upper right; stromal cells at lower left. The two components are separated by an incomplete-appearing basal lamina (reproduced by courtesy of Dr F. E. Dische and the Editor, Journal of Pathology) ($\times 1260$).

A broad hint comes from analyses of the phenotypic expression of the synovioocyte and chondrocyte. A clone of synovial cells or chondrocytes in culture might, it could be supposed, behave uniformly under uniform conditions. But cultural conditions cannot remain constant. When to changes in pH, redox potential, metabolite accumulation, and ageing are added physical, mechanical, or chemical disturbances we are not surprised that the morphology and physiology of the cultured cells change. The direction of change is determined by the nature of the stimulus. If under the influence of inherited, chemical, viral, immunological, or physical stimuli synovioblasts begin to multiply in the uncontrolled and purposeless manner characteristic of neoplasia it is surprising that in different individuals of distinct race, age, and sex and in a variety of anatomical situations the cancer cell should result in gross morphological disorders of widely differing appearance and behaviour?

Much the same argument may help us to understand the extraordinary diversity of disease forms that are identified chemically in or in relation to cartilage. As Sokoloff (1976) and his colleagues have shown in their experiments on chondrocyte culture the alteration from monolayer to spinner culture conditions determines large quantitative and important qualitative changes in the molecular species manufactured and exported by these cells. The genetic structure of the cell remains unaltered but a variety of metabolic, growth, and synthetic processes are derepressed, while others are switched-off. The consequences appear to the biologist to be as diverse as do the neoplastic or neoplastic-like cartilagenous diseases to the pathologist.

If it is supposed that all chondrocytes are endowed with identical genetic programmes then each should behave in an identical fashion under identical environmental circumstances. This can reasonably be assumed for a monoclonal cell culture. If the cells that come to form, say, a benign ecchondroma of the second metacarpal head in a young man multiply without purpose or control then it is entirely logical to deduce that changes in the local environment have promoted this disorderly, neoplastic growth. In a substantial number of instances of cartilagenous neoplasms there is clinical evidence of an underlying genetic defect. Although the chondrodystrophies, chondrodystrophia fetalis, and multiple ecchondromatosis all exhibit the criteria of inherited abnormality, and although chondroma and chondrosarcoma may originate on the basis of inherited disorders of cartilage, it seems certain that the true cartilagenous (and synovial) neoplasms are finally promoted by environmental stimuli the nature of which we are almost entirely unaware.

One explanation for the abnormal expression of neoplastic synovial and chondroid cells is a fault in the feed-back mechanisms by which the quantity or quality, or both, of matrix components regulates connective tissue cell gene expression. It is established that the extracellular matrix exerts an important role in regulating the synthetic and secretory activities of connective tissue cells (Grobstein, 1975). Much is now known of the synthesis of the extracellular matrix components, and there is growing understanding of the ways in which synthesis and secretion are regulated. It is also becoming clear that the macromolecules of the matrix themselves control cell activities such as glycosaminoglycan synthesis (Meier and Hay, 1975) and fibroblast migration (Toole, 1976). Comparable regulatory mechanisms affect chondrocyte behaviour, and collagenase or hyaluronidase, for example, increase macromolecular synthesis when added to chick rudiments in culture (Fitton-Jackson, 1970).

It may be reasonable to conclude that understanding of the origins and natural history of the connective tissue neoplasms will grow rapidly in the coming decade as knowledge of normal connective tissue cell behaviour increases. Nevertheless, compared with the efforts being expended to understand rheumatoid arthritis and osteoarthritis, present investigations of the pathological physiology of the neoplastic disorders seem relatively slight.

Classification of connective tissue diseases

The classification (Tables 4-11) and nomenclature of connective tissue diseases are among the controversial questions that remain of outstanding importance to diagnostic pathologists. As cell and biochemical genetics have advanced so more and more of the disorders attributable to mutant genes of large or small effect have been defined in terms of faults in limited parts of single structural or enzymic proteins or in other molecular species. For many years the

Table 4 *Inherited diseases of connective tissue*

Disease	Examples
Chromosomal abnormalities	
Mutant genes	
Dominant	Achondroplasia, polydactyly
Recessive	Many of the 'metabolic' disorders, congenital hypophosphatasia
Multifactorial	Some forms of secondary osteoarthritis, Perthes's disease
HLA-related	Ankylosing spondylitis, the 'reactive' arthritides

Table 5 *Inflammatory diseases of connective tissue*

Disease	Examples
Acute Lysosomal	Behçet's syndrome 'Storage' diseases
Chronic Inflammatory Fibrotic	Sarcoid, Crohn's disease Keloid, systemic sclerosis, Dupuytren's contracture, (may be familial, dominant characteristics), Peyronie's disease

Table 6 *Immunological diseases of connective tissue*

Disease	Examples
Hypersensitivity	Serum sickness, polyarteritis, nodular vasculitis, temporal arteritis, giant cell arteritis
Immune deficiency	Agammaglobulinaemia, Job's syndrome
Autoimmune	Systemic lupus erythematosus, rheumatoid arthritis, juvenile polyarthritis, rheumatic fever

Table 7 *Infective diseases of connective tissue*

Disease	Examples
Viral	Rubella, mumps, variola } arthritis
Bacterial	Chlamydial, gonococcal, staphylococcal, tuberculous } arthritis 'reactive' arthritides
Protozoal	Amoebiasis
Metazoal	Onchocerciasis
Fungal	Candida, nocardia } arthritis

Table 8 *Physical diseases of connective tissue*

Disease	Examples
Traumatic	Direct injury, fracture-associated haemorrhage (haemophilic)
Irradiation	x -Irradiation, γ -Irradiation, isotopic
Embolic	Caisson disease

Table 9 *Chemical diseases of connective tissue*

Disease	Examples
Regional, geographical	Kashin-Beck disease, endemic familial arthritis of Malnad
Occupational	Fluorosis
Therapeutic, iatrogenic	Osmic acid, radioactive gold, radioactive yttrium, bismuth arthropathy

Table 10 *Metabolic and nutritional diseases of connective tissue (many of the metabolic disorders are heritable)*

Disease	Examples
Disorders of nucleic acid metabolism	Gout
Disorders of collagen	Scurvy
Faults in hydroxylation	? Diabetic
Faults in glycosylation	glomerulosclerosis
Faults in procollagen peptidase	Floppy mitral valve syndrome (Ehlers-Danlos type)
Faults in cross-linking	Osteolathyrism, Menkes's kinky hair syndrome
Faults of uncertain aetiology	Marfan's syndrome, osteogenesis imperfecta, homocystinuria, alkaptonuria
Disorders of proteoglycan	The GAG storage diseases
Disorders of elastic material	Lathyrism
Disorders of basal laminae	Diabetes mellitus
Disorders of other proteins	Amyloid
Disorders of amino-acids	Alkaptonuria
Disorders of mineralisation	Chondrocalcinosis, apatite-deposition disease

Table 11 *Connective tissue diseases of ageing; and neoplastic, endocrine, and miscellaneous connective tissue diseases*

Diseases	Examples
Ageing	Osteoarthritis, intervertebral disc disease
Neoplastic (see Tables 1, 2, 3)	
Primary Benign	Haemangioma, lipoma, giant cell tumour
Malignant	Synovioma, clear cell sarcoma
Metastatic Neoplastic-like	Villonodular synovitis
Endocrine	
Pituitary	Acromegaly
Adrenal	Hyperadrenal corticoidism
Thyroid	Hypothyroidism
Parathyroid	Hyperparathyroidism
Miscellaneous	Seronegative arthritides, relapsing polychondritis, thalassaemic osteoarthritis, hypertrophic pulmonary osteosclerosis

term 'rheumatism' served a clinical purpose: it is no longer adequate. The phrase 'collagen disease' conveyed Klemperer's (1942) views on the nature of systemic lupus erythematosus and systemic sclerosis (Klemperer *et al.*, 1942): it has now been abandoned because of our failure to shown any primary disturbance of collagen in these and related diseases. However, understanding of the synthesis, export, and maturation of collagen, elastin, and the proteoglycans has led to the emergence of categories of disease that *are* properly termed diseases of collagen, elastin, the proteoglycans, and basal laminae. Stimulated by classifications such as those of McKusick (1972)*, it has become urgently necessary to rename many of the diseases of connective tissue to take account of our understanding of the primary defect. Just as McKusick paved the way with his concept of mucopolysaccharidoses so Lapière and Nussgens (1976) and Levene (1978a) have elegantly demonstrated that the new knowledge of collagen synthesis and maturation can be used to reclassify many other connective tissue diseases. Scurvy becomes a form of acquired proline hydroxylase deficiency, type VI Ehlers-Danlos syndrome becomes one form of lysyl hydroxylase deficiency, Menkes's disease becomes one of the defects of collagen cross-linking, and so on. Comparable logic is now applicable in the case of McKusick's own classifications. The cumbersome old term 'mucopolysaccharidosis' can be set on one side, and the inherited defects of the lysosomal hydrolases that culminate in inadequate degradation of the glycosaminoglycans can be grouped as the inherited glycosaminoglycan storage diseases. These can individually be termed, for example, α -L-iduronidase deficiency (IH), heparan N-sulphatase deficiency, N-acetylgalactosamine H-sulphatase deficiency (severe), and so on.

We are nearing the time when osteoarthritis, gout, rheumatoid arthritis, and intervertebral disc disease can be approached in a similar manner. Primary generalised osteoarthritis has long been separated from the so-called common secondary forms. We can now recognise clearly the pathological characteristics of such forms as idiopathic avascular femoral head necrosis, analgesic osteoarthritis, bismuth arthropathy, and neurogenic arthropathy. It is, I believe, only a matter of time before the inclusive word osteoarthritis comes to be regarded as no more

*McKusick (1976) claims that while 'the Mendelian disorders of collagen, elastin and mucopolysaccharide are the true disorders of connective tissue', others such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis 'are disorders in but not of connective tissue'. I do not believe that is an acceptable analysis.

than a synoptic term analogous to 'heart failure' or 'uraemia'—common descriptive names for superficially similar syndromes caused by a wide range of agents that have in common only an identical end stage.

Conclusion

Bindegewebe (connective tissues) were seen by Bichat and described by Johannes Muller. Fifty years after Bichat they formed the key with which Virchow unlocked the door of cellular pathology. In turn, they provided Klemperer with a logical explanation for common features shared by systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, dermatomyositis, and polyarteritis nodosa. The evidence available today allows us to predict even greater advances in knowledge of the connective tissue diseases during the years to come.

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