In several cases, fullness of the face suggestive of oedema, increase in abdominal girth, and sometimes very slight sacral oedema were noted. These cases were regarded with suspicion as possibly resulting from water retention due to the effects of cortisone. They occurred chiefly in cases with severe carditis, and in the milder cases similar doses of cortisone did not appear to have the same result. There was always an element of doubt, therefore, about how far the apparent water retention was due to cardiac failure and how far to the administration of the drug, but it was thought wise on occasion to use mercurial diuretics. In this small series of cases the blood electrolyte values were not very helpful, and in those children who were gravely ill the measurement of fluid intake and output had practical difficulties which diminished its accuracy.

It would appear that fullness of the face and abdomen was not always due to water retention, as it might occur without any disturbance of the fluid balance or blood electrolytes. In these cases the texture of the subcutaneous tissues, particularly the abdominal wall, suggested increased deposition of fat and was often associated with a voracious appetite, during and for some time after cortisone administration.

The investigations confirmed the results of other workers—that cortisone exerts a beneficial effect upon non-cardiac manifestations of rheumatic fever—for example, pyrexia, raised sedimentation rate, and articular inflammation—though it is doubtful if the joints respond more favourably than to salicylates.

The dosage of cortisone varied from 50 mg. to 500 mg. daily over periods of a few days to a few weeks. A fall in the eosinophil count was taken as evidence that the particular batch of cortisone was active.

The results of cortisone treatment were, on the whole, disappointing, and high dosage did not appear to achieve anything more than moderate dosage and carried with it a greater risk of side-effects. Whilst admitting the lack of any spectacular response, we think that the improvement in the patient's general condition and the tendency to slowing of the heart justify further investigation. It would appear that more information is necessary about the effects of prolonged administration of small doses, particularly if there is an initial beneficial response to moderate doses. Such treatment would obviously need careful supervision, cautious dosage, and the use of mercurial diuretics from time to time, if necessary.

We wish to express our appreciation of the help from our colleagues, both medical and nursing. In particular we would like to thank our medical registrars—Dr. McKendrick, Dr. Anderton, Dr. Jones, Dr. Ellenbogen, and Dr. Coulshed—and the resident medical officers of our various hospitals. For electrocardiographic records we are indebted to the careful work of Mr. E. Caldwell.

NOTE.—The case histories, in fuller and more detailed form, will be available on duplicated sheets from the office of the *British Medical Journal* to those who express a special interest in having them.

REFERENCES

Barnes, A. R., and Smith, H. L. (1950). *Mod. Conc. cardio-vasc. Dis.*, 19, 59.
Bell, G. I., Bell, R. E., and Wilson, D. R. (1950). *Canad. med. Ass. J.*, 63, 63.
Coste, F., *et al.* (1950). *Bull. Soc. méd. Hôp. Paris*, 66, 1577.
Craige, E., *et al.* (1950). *Circulation*, 1, 1338.
Fox, T. T., *et al.* (1950). Ibid., 1, 1184.
Harris, T. N., *et al.* (1951). Ibid., 3, 215.
Hench, P. S., Kendall, E. C., *et al.* (1950). *Arch. intern. Med.*, 85, 545.
—— Slocumb, C. H., *et al.* (1949). *Proc. Mayo Clin.*, 24, 277.
Keith, John D., and Neill, C. A. (1951). *Canad. med. Ass. J.*, 64, 193.
McEwen, C., *et al.* (1950). *Bull. N.Y. Acad. Med.*, 26, 212.
Taram, L. M., and Szilagyi, N. (1951). *Brit. Heart J.*, 13, 10.
Videbaek, A., *et al.* (1950). *Acta endocrinol.*, 4, 245.

SOME CONCEPTS OF RHEUMATIC DISEASE*

BY

J. H. KELLGREN, M.B., F.R.C.S., M.R.C.P.

Reader in Rheumatic Diseases and Clinical Director, Rheumatism Research Centre, University of Manchester

The normal and morbid anatomy of the connective tissues at the molecular level has been discussed in some detail because it is at this level, where structure and function are inseparable, that the essential processes of life arise, and because I believe that it is through discoveries at this level that revolutionary advances in our understanding of the rheumatic diseases are likely to take place.

At the clinical level patients suffering from the rheumatic diseases present a variety of disorders of structure and function, and we will now examine some of these disorders more closely to see whether or not they can be fitted into a concept of rheumatic diseases based upon the assumption that these diseases result from primary connective-tissue lesions.

Some of the most prominent features of two typical rheumatic diseases, such as rheumatoid arthritis and degenerative joint disease, are set out in Table I. The clinical features of degenerative joint disease clearly result from the initial cartilage lesion, but the manifold features of rheumatoid disease present a more complex problem. But before discussing the various features of rheumatoid disease it would be as well to define this clinico-pathological entity. In many countries, and particularly in America, the term has been used to embrace all forms of polyarthritis of obscure aetiology, so including ankylosing spondylitis, psoriatic arthropathy, Reiter's disease, and many other polyarthritic syndromes, as well as the classical form of rheumatoid disease with symmetrical peripheral joint involvement, widespread soft-tissue changes, and other features mentioned in Table I.

TABLE I

Clinical Features	Rheumatoid Disease	Degenerative Joint Disease
Connective tissue lesions	Widespread, often symmetrical, affecting joints, tendons, bones, muscles, skin, viscera, eyes, and other structures. Resulting in marked atrophy and destruction of all affected structures	Often localized to one or more joints, resulting in loss of cartilage and bone in pressure zones with marginal overgrowth
Serum factor agglutinating sensitized sheep cells	Present in high titre in most cases	No more than normal
Loss of body weight ..	Marked, particularly during exacerbations of disease	None
Inflammatory reaction	Marked, both locally in connective tissues as well as systemically	Very little if at all, and only locally in joints
Lymphadenopathy ..	Frequent, particularly in young subjects; occasional splenomegaly	None
Anaemia	Frequent, particularly during exacerbation of disease	,,
Personality changes ..	Frequent during exacerbation of disease	,,
Increased sweating and peripheral vascular disorders	Marked, particularly during exacerbation of disease	,,
Course of disease ..	Very variable with many unexpected exacerbations and remissions	Usually slowly progressive

*The second Goulstonian Lecture, given at the Royal College of Physicians of London on January 17. The first lecture was published in our previous issue.

In this country ankylosing spondylitis has always been recognized as a separate disease. Reiter's disease is also distinguished from rheumatoid arthritis by its clinical features and definite epidemiology (Paronen, 1948). Psoriatic arthropathy also has distinctive clinical features and is often diagnosed as such, but after eliminating typical examples of these three well-defined conditions from the rheumatoid group we are still left with a mass of polyarthritic and other diseases which does not present an altogether homogeneous picture and which is very likely made up of rheumatoid disease proper, together with a number of other as yet undefined arthritic syndromes and atypical examples of those that we have already defined. In our unit we have always tried to separate as many as possible of the "atypical" cases from the main group of rheumatoid disease, and the recent clearer definition of the clinical features of primary generalized osteoarthritis (Kellgren and Moore, 1952) has undoubtedly helped to remove a number of cases which might previously have been placed in the rheumatoid group. Nevertheless, there are many cases in which no satisfactory diagnosis can be made on clinical grounds, and the introduction of some specific diagnostic aid would be of real help.

The Agglutination Reaction

In 1948 Rose and his co-workers noted that serum from patients with rheumatoid disease agglutinated sensitized sheep cells in a higher dilution than did serum from subjects not suffering from rheumatoid disease. This finding was confirmed by other workers (Sulkin *et al.*, 1949; Jawetz and Hook, 1950). Technical improvements designed to eliminate the effects of heterophil antibody and other sources of error were introduced by Heller, Jacobson, and Kolodny (1949) and by Ball (1950); and since 1949 this test has been used extensively in our unit, the serological test being carried out blindly by Dr. Ball in the laboratory and his results being subsequently compared with the clinical diagnoses made in the wards and out-patient clinics. Between April, 1949, and November, 1950, the test was carried out on serum from 1,943 individuals, and the analysed results are shown in Table II. It will be seen that the incidence of positive reactions was uniformly low, except in the "rheumatoid" group, where it was 47.4%.

TABLE II.—*Results of Agglutination Test in Rheumatoid Arthritis and Other Diseases*

Disease	Total No.	Positive	
		No.	% of Total
Rheumatoid arthritis	642	304	47·4
Ankylosing spondylitis	203	3	1·5
Osteoarthritis	249	8	3·2
Other arthritides	289	19	6·6
Obscure painful states	176	4	2·3
Rheumatic fever and acute and subacute rheumatism	47	0	0
Non-arthritic disease and normal	337	3	0·9
Non-rheumatoid total	1,301	37	2·8

TABLE III.—*Results of Agglutination Test in Various Subgroups of Rheumatoid Arthritis*

Subgroup	Total No.	Positive	
		No.	% of Total
Total	642	304	47·4
Males	178	109	61·2
Females	464	195	42·0
Subcutaneous nodules present	96	77	80·2
No x-ray abnormality found	57	12	21·1
Central joints only involved	25	1	4·0
Associated with psoriasis	14	1	7·1

From the clinical standpoint it was recognized that this "rheumatoid" group was unlikely to be homogeneous, and a further analysis of these 642 "rheumatoid" cases is shown in Table III. It will be seen that in cases with subcutaneous nodules, which are indisputable examples of rheumatoid disease, the proportion of positive agglutination reactions is as high as 80%, while in cases of "polyarthritis" associated with psoriasis and in those without involvement of the peripheral joints positive agglutination reactions were only rarely observed.

Table IV represents a further analysis of the cases classed as other arthritides in Table II, and it will be seen that the relatively high proportion of positive reactions in this group is largely due to cases of disseminated lupus erythematosus, scleroderma, and dermatomyositis, and to a few cases in which the diagnosis was uncertain.

TABLE IV.—*Results of Agglutination Test in Various Arthritides*

Clinical Type	Total No.	No. Positive
Indeterminate arthritis	82	4
Disk lesions	51	0
Gout	18	1
"Infective" arthritis	17	2
Shoulder syndromes	13	0
Tuberculous arthritis	12	0
Disseminated lupus erythematosus	10	6
Atypical polyarthritis	9	2
Scleroderma	7	2
Acromegaly	6	0
Intermittent hydrarthrosis	6	0
Reiter's syndrome	5	0
Gonococcal arthritis	4	0
Osteochondritis	4	0
Tuberculosis and rheumatism	4	0
Periarteritis nodosa	3	0
Allergic arthritis	3	1
Hypertrophic pulmonary osteo-arthropathy	3	0
Dermatomyositis	3	1
Syphilitic arthritis	3	0
Erythema nodosum	2	0
Haemarthrosis	1	0
Myelomatosis	1	0
Morquio's syndrome	1	0
Miscellaneous	21	0
Total	289	19

Thus a positive agglutination reaction is usually found in cases of classical rheumatoid arthritis, disseminated lupus erythematosus, and possibly in dermatomyositis and scleroderma—a group of diseases in which the fibrinoid connective-tissue change is characteristically found and in which intermediate and apparently indistinguishable clinical variants are quite common. On the other hand, the agglutination reaction appears to be uniformly negative in rheumatic fever, although fibrinoid change is equally characteristic of this disease. It is, however, by no means certain that the transient fibrinoid of rheumatic fever and the more permanent fibrinoid of the rheumatoid group are in fact identical, and its association with streptococcal infection and its distinct clinical features are excellent reasons for placing rheumatic fever in an entirely separate category. Thus the potential value of the agglutination reaction is its apparent capacity for distinguishing rheumatoid disease from other atypical and as yet undefined polyarthritic syndromes.

Let us now return to the consideration of rheumatoid arthritis, including only those typical cases in which fibrinoid lesions and a positive agglutination reaction are commonly found, and excluding the various atypical polyarthritic syndromes. The following statements about this disease are largely based upon my own personal experience of some 700 cases taken from a total of over 2,000 cases of arthritis of all types seen in this department during the past four years.

Connective-tissue Atrophy and Weight Loss

The fibrinoid lesion of the connective tissues has already been dealt with, but an equally characteristic feature of rheumatoid disease is the widespread atrophy of bone, cartilage, tendon, skin, and other collagenous structures. Indeed,

Goldthwait (1904) was so impressed with this atrophy that he introduced the term "atrophic arthritis." That these atrophic changes are not entirely due to disuse is clear from the fact that they may be seen in symptomless limbs, and in patients who have always been fully employed; and, indeed, the most severe atrophy may be seen in those courageous patients who have continued to live a most active life in spite of severe and widespread disease. In other conditions an inflammatory tissue reaction tends to heal by the formation of new connective tissue, leading to scarring, but in rheumatoid disease inflammatory reactions seem to be followed by loss of tissue substance and further atrophy, so that the supporting structures of the body seem to melt away, giving rise to those pathetic withered limbs which are so characteristic of this disease.

If our interpretation of the fibrinoid lesion is correct the collagen is lost after disintegration of the normal connective-tissue complex; and where a sizable portion of this complex is destroyed an insoluble residue rich in polysaccharides is left behind. But there is no reason why a molecular disintegration should not take place in a widespread manner throughout the connective tissue without the formation of appreciable quantities of residue, and such a process would certainly explain the widespread connective-tissue atrophy. Although this atrophy is usually progressive in rheumatoid arthritis a temporary reduction of body weight amounting to 2 to 3 stone (12.7 to 19.1 kg.) is a common finding in the early stages of the disease, and this may recur with each exacerbation of the rheumatoid process; the patients, however, usually regain their normal body weight during remissions and may even do so in spite of continuing disease. Part of this weight loss is probably due to low food intake resulting from the loss of appetite that accompanies the personality changes, which are discussed later, but attempts to combat it with special diets, forced feeding, insulin, and other means have not proved very effective. Whether the weight loss results from a mobilization of body protein in an attempt to replace the disintegrating collagen or whether it simply represents the excessive catabolic activity which accompanies tissue injury of all kinds is not clear. With the subsidence of the rheumatoid process the metabolic demands appear to be reduced and body fat, muscle, and other proteins which take part in the metabolic pool are rapidly re-formed, but owing to the very slow turnover of connective-tissue collagen re-formation of these tissues is less complete.

The Inflammatory Reaction

The inflammatory reaction, both local and systemic, accounts for many of the most striking symptoms of rheumatoid disease, such as pain, swelling, stiffness, fever, toxaemia, lymphadenopathy, and the plasma protein changes which form the basis of the sedimentation rate and many other tests. Certain changes in the connective-tissue polysaccharides, such as those leading to loss of viscosity in the synovial fluid (Ropes *et al.*, 1947; Ragan and Meyer, 1949) and to abnormal metachromatic staining of the connective tissues (Altshuler and Angevine, 1949), may also be part of this reaction.

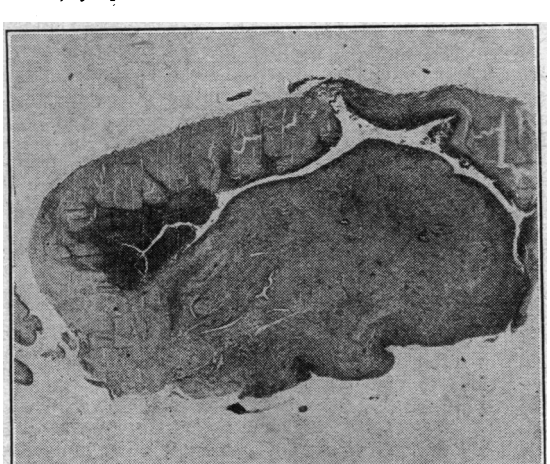

FIG. 4.—Transverse section of rheumatoid tendon lesion (stained H. and E.) (×10), illustrating relation of fibrinoid change (dark areas) to inflammatory and proliferative reaction.

The local inflammatory reaction and its relation to the fibrinoid change is well seen in the tendon lesions which are such a feature of rheumatoid disease (Kellgren and Ball, 1950). A typical example is shown in Fig. 4, which is a transverse section through part of one of the long flexor tendons of a finger. A few of the original tendon bundles have undergone fibrinoid change; adjacent to these is a mass of inflammatory granulation tissue which is also undergoing fibrinoid change in some parts. In the synovial cavities the inflammation is more widespread and its relation to fibrinoid lesions is less obvious, but they can usually be found if looked for systematically. It has generally been assumed that the fibrinoid and other connective-tissue changes result from the inflammatory reaction, but a case can be made for the opposite view.

The idea that many features of the inflammatory reaction are produced by substances liberated from damaged tissue is not new and was studied extensively by Sir Thomas Lewis (1927, 1942). More recently Moon and Tershakovec (1951) have reached the same conclusion from experiments on animals. Furthermore, Menkin (1947) has shown that inflammatory exudates contain substances which reproduce both the local and the systemic features of the inflammatory reaction, and that these substances are mostly simple peptides. If the initial lesion of rheumatoid disease is a disruption of the collagen-polysaccharide complex, together with a disintegration of the collagen molecule, a considerable number of peptides are likely to be liberated, since the collagen macro-molecule is built out of peptide chains, and it is quite possible that one or more of these peptides may have toxic properties similar to those of Menkin's peptide fractions from inflammatory exudate. Thus the inflammatory and toxic features of rheumatoid arthritis could conceivably result from a primary disintegration of collagen. Admittedly there is no direct evidence in support of this view at the moment, but it is clearly a possibility which requires investigating.

Anaemia is a very frequent finding in rheumatoid disease. It is usually of the toxic suppressive type of only moderate severity and accompanied by leucopenia. This anaemia clears up with remission of the rheumatoid process, or during suppression of its toxic and inflammatory features by cortisone or A.C.T.H. therapy, but is otherwise resistant to treatment. In some cases there may also be an iron-deficiency anaemia which will respond only to very large doses of iron given preferably by the intravenous route (Sinclair and Duthie, 1950). Much more than the calculated iron deficit must be administered, since iron utilization is interfered with as in other diseases accompanied by long-standing inflammatory changes (Slack and Wilkinson, 1949). Thus both forms of anaemia would appear to be part of the toxaemia and the inflammatory reaction.

Personality changes are a common feature of rheumatoid disease. They are usually found in patients with severe and widespread disease, and may be one of the presenting symptoms of this condition. Although they are most commonly found in patients who were previously unstable, this is not invariably the case, and an apparently normal individual may become depressed, irritable, and emotionally unstable, tending to weep at the slightest provocation. At this stage there is often marked loss of appetite and a weight loss of a stone (6.4 kg.) or more, and the sedimentation rate is considerably raised; joint symptoms, however, may be quite trivial. With the progress of the disease these personality changes often recover, in spite of increasing crippling, but they usually recur with the onset of each exacerbation of the rheumatoid process. The fact that these personality changes may be a presenting symptom excludes

the possibility of their being the result of chronic crippling disease in these cases, and it seems more likely that they are analogous to the toxic personality changes which accompany diseases such as hepatitis and influenza. Certainly the administration of cortisone and A.C.T.H. appears to have a most striking and immediate effect on these changes, even in those cases in which the crippling joint disease remains largely unaffected.

Disorders of the peripheral circulation are common in rheumatoid disease and may be one of its presenting features. We have made a special study of this aspect of rheumatoid disease (Janus, 1952), and it appears that this disturbance is complex, consisting in a decrease of cutaneous blood flow, particularly in the extremities, together with an increase of deep blood flow in the limbs, especially in severely affected joints. There is also an increased cardiac output as judged by ballistocardiographic observations. The cutaneous flow may be increased by sympathectomy and the disturbance of cutaneous and deep flow, and cardiac output may be corrected by the administration of cortisone or A.C.T.H. Although the exact mechanism of these disturbances has not been fully worked out, their relief by cortisone and A.C.T.H. suggests that a chemical disorder is involved at some stage.

There are other clinical features of rheumatoid disease which might be discussed, such as changes in skeletal muscle, visceral, ocular, and cutaneous manifestations, the occasional occurrence of amyloid disease, and so on; but these must be left to another occasion, since we still have the role of the adrenal cortex to consider.

The Adrenal Cortex

When Hench *et al.* (1949) first demonstrated the remarkable effects of cortisone upon many of the features of rheumatoid disease it seemed as if the adrenal cortex must play some central part in the pathogenesis of this disease. But it very soon became apparent that the clinical features of many other diseases could be strikingly modified by giving cortisone or A.C.T.H. Furthermore, patients with demonstrable disorders of the adrenal cortex do not suffer specially from rheumatoid disease. The role of the cortical hormones is therefore best considered in the light of their general homoeostatic functions, which have been recently reviewed by Sayers (1950).

The results of many experiments on animals, together with the experience gained from the administration of cortisone and A.C.T.H. to patients suffering from all kinds of diseases, have led to the following conclusion. The pituitary adrenocortical system responds rapidly to any stress by the production of relatively large amounts of steroids similar to or identical with compound F and cortisone. The effects of large amounts of these steroids produced endogenously or administered from without are manifold, but they concern chiefly the body's reactions to insults of various kinds. Thus these steroids interfere with wound-healing (Ragan, Grokoest, and Boots, 1949; Ragan, Howes, *et al.*, 1949; Baker and Whitaker, 1950; Bangham, 1951), with the repair of fractures (Blunt *et al.*, 1950), and with the local inflammatory response to trauma and chemical irritants (Jones and Meyer, 1950; Michael and Whorton, 1951; Shapiro *et al.*, 1951). They reduce both the local and the systemic inflammatory reactions to infection with bacteria or virus (Kass *et al.*, 1950; Kass and Finland, 1951), and this may have deleterious effects, particularly in tuberculosis (Hart and Rees, 1950). They also suppress the clinical features of allergic disease (Randolph and Rollins, 1950; Carey *et al.*, 1950) and interfere with the tuberculin reaction (Long and Miles, 1950) and the Arthus phenomenon (Germuth and Ottinger, 1950), and they modify the reaction to tissue homografts (Billingham, Krohn, and Medawar, 1951).

Whether the cortical steroids prevent damaged tissues from liberating the substances normally responsible for the inflammatory and allergic reactions and the processes of healing, or whether they neutralize or destroy these substances, or protect intact tissues against their action, is as yet uncertain; but it has been established that their main action is a local one in the tissues themselves.

Cortisone and A.C.T.H.

In rheumatoid disease the administration of cortisone and A.C.T.H. produces a striking and prompt relief of symptoms in most cases. Thus spontaneous pain is usually relieved, and joint tenderness is markedly reduced, and this results in a striking improvement of function in the limbs. Local warmth and swelling are also reduced, and the reduction in swelling may be rapid and complete when the swelling is due to an excess of fluid in the joints and other structures. Fever and the other constitutional features of the toxaemia and inflammatory reaction may also be controlled, but the diseased connective tissues do not appear to return to a fully normal condition (Hench *et al.*, 1950) and cellular changes may persist, although symptoms such as pain have been adequately suppressed (Johnson, 1950).

Where the active disease process is of slight severity and limited extent patients can be kept symptom-free or almost so for months or even years by continuous hormone therapy (Boland and Headley, 1950; Ward *et al.*, 1951); but, where the active disease process is severe and widespread, satisfactory relief can often be obtained only by employing a dosage high enough to produce definite signs of hypercorticism. In this context it must be remembered that severe anatomical changes in the joints and other tissues may be found in patients in whom the disease process has become largely inactive. Furthermore, we have found that the degree of response to cortisone and A.C.T.H. varies greatly from one patient to another quite apart from the extent of their disease.

Although the administration of cortisone or A.C.T.H. in high enough dosage seems to suppress most of the symptoms of rheumatoid disease in the majority of patients, only a small proportion of these patients can obtain a really worth-while relief with a hormonal dosage which can be safely continued for long periods, and the effect of such suppressive therapy upon the long-term evolution of the rheumatoid disease process remains to be evaluated.

There are, however, some features of rheumatoid disease which appear to be less readily altered by the administration of cortisone or A.C.T.H. Thus in rheumatoid nodules removed from patients who have had intensive courses of these hormones we have seen the usual fibrinoid core which differs little from that seen in similar nodules before treatment. On the other hand, the surrounding zones of inflammatory and proliferative reaction were much less evident during hormone therapy. Similar findings have been reported by Hunt and Blanchard (1951) and Fienberg and Colpoys (1951), though they claim that the fibrinoid itself was reduced during prolonged and intensive hormone therapy and that it became more evident again after hormone withdrawal.

We have not seen any recovery of generalized connective-tissue atrophy during hormone therapy, and no reports of such recovery are available. Indeed, it would be surprising if such a recovery were to take place, since connective-tissue atrophy is one of the features of hypercorticism (Albright and Reifenstein, 1948).

The agglutination reaction shows no consistent change during cortisone or A.C.T.H. therapy according to Ragan, Grokoest, and Boots (1949), and Svartz and Schlossmann (1950), and our own findings are in agreement with this.

Thus there are features of rheumatoid disease which do not appear to be readily relieved by the adrenocortical hormones, and these features may well be closely related to the essential rheumatoid process, which apparently remains unaffected by hormone therapy. The dramatic change in the clinical picture which can often be produced by the administration of cortisone or A.C.T.H. in patients

with rheumatoid disease may very well be due to the suppression of the body's reaction to the essential rheumatoid lesion, the clinical picture in a given patient at any one time being the product of the connective-tissue disease, the body's reaction to this, and the suppressing activity of the pituitary-adrenal system or administered cortisone and A.C.T.H. Since each of these may vary independently it is not surprising that the clinical course of rheumatoid disease is so variable and so full of pleasant and also unpleasant surprises.

Other Factors

It is generally agreed that salicylates have a profound effect upon the inflammatory features of rheumatic fever. In rheumatoid disease they seem to have a much smaller but definite effect, and for some obscure reason aspirin appears to be more effective than sodium salicylate. If the dosage is pushed to the limits of tolerance some relief of pain and swelling is obtained in most cases, and in a few the relief is marked and comparable to that obtained in rheumatic fever. In these responsive cases relief of pain and swelling is accompanied by an increase of cutaneous blood flow and a rising eosinophil count (Janus, 1950). These findings suggest that aspirin has more than an analgesic action, and the rising eosinophil count makes it most unlikely that the relief of symptoms is due to adrenocortical stimulation.

From clinical observations it is clear that trauma and excessive wear and tear have a very adverse effect upon the disease process, and may even precipitate a local or general exacerbation. Indeed, the localized rheumatoid disease which may follow trauma in susceptible subjects causes frequent disputes over matters of compensation. Conversely, rest is beneficial. Where disease activity is localized, local rest may be obtained with appropriate plaster splintage, but where the disease is generalized rest in bed is essential. It is not yet clear whether rest acts upon the connective-tissue lesion or upon the inflammatory reaction, but its good effects are commonly long-lasting, which suggests that it may influence the course of the essential rheumatoid process. Rest has a favourable effect only upon the active disease process; when this has settled down and the patient is left with stiff joints and wasted muscles, active exercise, physiotherapy, and the whole rehabilitation programme which can be provided so well at our spas are all invaluable aids in regaining function and preparing the patient for a return to active life.

In the three controlled trials of gold therapy which have been carried out to date (Ellman *et al.*, 1940; Fraser, 1945; Adams and Cecil, 1950) the cases receiving gold showed a greater degree of improvement than the control group, and this has been our own experience. Thus gold salts may well have some influence upon the rheumatoid disease process, but their mode of action remains obscure.

The search for aetiological factors continues, and has so far been unsuccessful, but with a clearer understanding of the essential lesion of rheumatoid disease this search may possibly be directed into more fruitful channels.

Summary and Conclusions

The views expressed in these lectures may be summarized in the following concepts:

(1) The rheumatic diseases are essentially diseases of the supporting system of the body. This system is made up of connective tissues in varying degrees of organization, and it is mainly through a closer study of these tissues and the processes which maintain them that we shall come to understand and control this group of diseases.

(2) The intercellular collagen-polysaccharide complex is the functionally essential part of the connective tissues, and it is tentatively suggested that a disorder of this complex may be the primary lesion in both rheumatoid arthritis and degenerative joint disease.

(3) In rheumatoid disease there may be a loosening of the collagen-polysaccharide complex which allows the collagen molecule to disintegrate into relatively simple peptides which diffuse out of the affected tissue. When relatively large portions of tissue are affected a residual material rich in polysaccharide, and probably a glycoprotein, replaces the damaged tissue, thus producing the fibrinoid lesions. Some of the disintegration products of collagen may have toxic properties, and it is possible that these may account for some if not all of the manifold toxic and inflammatory features of rheumatoid disease.

(4) In degenerative joint disease the primary lesion appears to be a loss of chondroitin sulphate from the articular cartilage. This leaves the collagen fibrils unsupported, so that they may become changed and broken up with wear and tear. No toxic substances appear to be liberated during this process, and the clinical features of the disease are mainly due to mechanical disorganization of the affected joints.

These concepts are clearly gross over-simplifications and will probably have to be modified or even changed altogether as new data become available, since at this moment many brilliant workers are attacking these problems with a variety of new technical weapons. Nevertheless some synthesis of all the work done must be attempted from time to time if only to provide us with some definite point of view from which we may be able to see new and possibly more fruitful lines of investigation.

References

Abramson, D. J., and Kamberg, S. (1949). *J. Bone Jt Surg.*, 31A, 275.
Adams, C. H., and Cecil, R. L. (1950). *Ann. intern. Med.*, 33, 163.
Albright, F., and Reifenstein, E. C. (1948). *Parathyroid Glands and Metabolic Bone Disease*, p. 165. Williams and Wilkins Co., Baltimore.
Altshuler, C. H., and Angevine, D. M. (1949). *Amer. J. Path.*, 25, 1061.
Askanazy, M. (1921). *Virchows Arch.*, 234, 111.
Astbury, W. T. (1940). *J. int. Soc. Leath. Chem.*, 24, 69.
—— (1947). *Proc. roy. Soc. B*, 134, 303.
Baker, B. L., and Whitaker, W. L. (1950). *Endocrinology*, 46, 544.
Ball, J. (1950). *Lancet*, 2, 520.
—— (1952). In press.
Bangham, A. D. (1951). *Brit. J. exp. Path.*, 32, 77.
Bauer, W., and Bennett, G. A. (1936). *J. Bone Jt Surg.*, 18, 1.
Bear, R. S. (1942). *J. Amer. chem. Soc.*, 64, 727.
Billingham, R. E., Krohn, P. L., and Medawar, P. B. (1951). *British Medical Journal*, 1, 1157; 2, 1049.
Blunt, J. W., Plotz, C. M., Lattes, R., Howes, E. L., Meyer, K., and Ragan, C. (1950). *Proc. Soc. exp. Biol., N.Y.*, 73, 678.
Boland, E. W., and Headley, N. E. (1950). *J. Amer. med. Ass.*, 144, 365.
Bowes, J. H., and Kenten, R. H. (1948). *Biochem. J.*, 43, 358.
Bresler, S. E., Finogenov, P. A., and Ya Frenkel, S. (1950). *Doklady Akad. Nauk. S.S.S.R.*, 72, 555.
Buzagh, A. von (1942). *Kolloid Z.*, 101, 149.
Bywaters, E. G. L. (1937). *J. Path. Bact.*, 44, 247.
Carey, R. A., Harvey, A. M., Howard, J. E., and Wagley, P. F. (1950). *Bull. Johns Hopk. Hosp.*, 87, 354, 387.
Chain, E., and Duthie, E. S. (1940). *Brit. J. exp. Path.*, 21, 324.
Consden, R., Glynn, L. E., and Stanier, W. M. (1952). *Biochem. J.*, 50, xix.
Duran-Reynals, F. (1942). *Bact. Rev.*, 6, 197.
Ellman, P., Lawrence, J. S., and Thoroid, G. P. (1940). *British Medical Journal*, 2, 314.
Fagge, C. H. (1877). *Trans. path. Soc. Lond.*, 28, 201.
Fienberg, R., and Colpoys, F. L. (1951). *Amer. J. Path.*, 27, 925.
Fraser, T. N. (1945). *Ann. rheum. Dis.*, 4, 71.
Garrod, A. E., Allbutt, T. C., and Rolleston, H. D. (1907). *System of Medicine*, vol. 3. Macmillan, London.
Germuth, F. G., and Ottinger, B. (1950). *Proc. Soc. exp., Biol., N.Y.*, 74, 815.
Gersh, I., and Catchpole, H. R. (1949). *Amer. J. Anat.*, 85, 457.
Goldthwait, J. E. (1904). *Boston med. surg. J.*, 151, 529.
Hale, C. W., (1946). *Nature, Lond.*, 157, 802.
Hart, P. D'A., and Rees, R. J. W. (1950). *Lancet*, 2, 391.
Heberden, W. (1802). *Commentaries on the History and Cure of Disease*. T. Payne, London.
Heine, J. (1926). *Virchows Arch.*, 260, 521.
Heller, G., Jacobson, A. S., and Kolodny, M. H. (1949). *Proc. Soc. exp. Biol., N.Y.*, 72, 316.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, 24, 181.
—— —— —— —— (1950). *Arch. intern. Med.*, 85, 545.
Hirsch, C. (1944). *Acta chir. scand.*, 90, Suppl. 83.
Hunt, T. E., and Blanchard, A. J. (1951). *Ann. Rheum. Dis.*, 10, 337.
Janus, O. (1950). *British Medical Journal*, 2, 1244.
—— (1952). In preparation.
Jawetz, E., and Hook, E. V. (1950). *Proc. Soc. exp. Biol., N.Y.*, 70, 650.
Johnson, R. W. (1950). *J. Bone Jt Surg.*, 32A, 475.
Jones, I. S., and Meyer, K. (1950). *Proc. Soc. exp. Biol., N.Y.*, 74, 102.
Kass, E. H., and Finland, M. (1951). *New. Engl. J. Med.*, 244, 464.
—— Ingbar, S. H., and Finland, M. (1950). *Ann. intern. Med.*, 33, 1081.

Kellgren, J. H., and Ball, J. (1950). *Ann. rheum. Dis.*, **9**, 48.
—— —— Astbury, W. T., Reed, R., and Beighton, E. (1951). *Nature, Lond.*, **168**, 493.
—— and Moore, R. (1952). *British Medical Journal*, **1**, 181.
Klemperer, P. (1950). *Amer. J. Path.*, **26**, 505.
Klinge, F. (1933). *Ergebn. Path.*, **27**, 1.
—— (1934). *Handb. spez. path. Anat. Hist.*, edited by O. Lubarsch, and F. Henke, vol. 9/2, p. 107. Springer, Berlin.
Lewis, T. (1927). *Blood Vessels of the Human Skin and their Responses* London.
—— (1942). *Pain*. MacMillan Co., New York.
Lison, L. (1935). *C.R. Soc. Biol., Paris*, **118**, 821.
Long, D. A., and Miles, A. A. (1950). *Lancet*, **1**, 492.
McManus, J. F. A. (1946). *Nature, Lond.*, **158**, 202.
Mau, C. (1929). *Z. orthop. Chir.*, **51**, 106.
Menkin, V. (1947). *Lancet*, **1**, 660.
Meyer, K. (1947). *Physiol. Rev.*, **27**, 335.
—— (1950). *Connective Tissues*, p. 88. Trans. 1st Conf. Josiah Macey Foundation, New York.
Michael, M., and Whorton, C. M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 754.
Moon, V. H., and Tershakovec, G. A. (1951). *Arch. Path.*, **52**, 369.
Nageotte, J. (1927). *C.R. Acad. Sci.*, **184**, 115.
Neuberger, A., Perrone, J. C., and Slack, H. G. B. (1951). *Biochem. J.*, **49**, 199.
Neuman, R. E., and Logan, M. A. (1950). *J. biol. Chem.*, **184**, 299.
Neumann, E. (1880). *Arch. mikr. Anat.*, **25**, 130.
Paronen, I. (1948). *Acta med. scand.*, Suppl. 212.
Partridge, S. M. (1943). *Biochem. J.*, **43**, 387.
Penney, E. J. R., and Balfour, B. M. (1949). *J. Path. Bact.*, **61**, 171.
Perrone, J. C., and Slack, H. G. B. (1951). *Biochem. J.*, **49**, lxxii.
Porter, K. R., and Vanamee, P. (1949). *Proc. Soc. exp. Biol., N.Y.*, **71**, 513.
Ragan, C., Grokoest, A. W., and Boots, R. H. (1949). *Amer. J. Med.*, **7**, 741.
—— Howes, E. L., Plotz, C. M., Meyer, K., and Blunt, J. W. (1949). *Proc. Soc. exp., Biol., N.Y.*, **72**, 718.
—— and Meyer, K. (1949). *J. clin. Invest.*, **28**, 56.
Randolph, T. G., and Rollins, J. P. (1950). *J. Allergy*, **21**, 260.
Rich, A. R., and Gregory, J. E. (1943). *Bull. Johns Hopk. Hosp.*, **72**, 65.
Ropes, M. W., Robertson, W. B., Rossmeisl, E. C., Peabody, R. B., and Bauer, W. (1947). *Acta med. scand.*, Suppl. 196.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol., N.Y.*, **68**, 1.
Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
Scaglietti, O., and Casuccio, C. (1936). *Chir. Organi Mov.*, **20**, 469.
Schmitt, F. O., Hall, C. E., and Jakus, M. A. (1942). *J. cell. comp. Physiol.*, **20**, 11.
Selye, H. (1950). *Stress*. Acta Inc., Montreal.
Shapiro, R., Taylor, B., and Taubenhaus, M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 854.
Sinclair, R. J. C., and Duthie, J. J. R. (1950). *British Medical Journal*, **2**, 1257.
Slack, H. G. B., and Wilkinson, J. F. (1949). *Lancet*, **1**, 11.
Sulkin, S. E., Pike, R. M., and Coggeshall, H. C. (1949). *Proc. Soc. exp. Biol., N.Y.*, **70**, 475.
Svartz, N., and Schlossmann, K. (1950). *Ann. rheum. Dis.*, **9**, 377.
Sydenham, T. (1676). *Works of Thomas Sydenham, M.D.* Translated from Latin edition by Greenhill, 1848. London.
Sylvén, B. (1941). *Acta chir. scand.*, Suppl. 66.
—— Paulson, S., Hirsch, C., and Snelman, O. (1951). *J. Bone Jt Surg.*, **33A**, 333.
Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S. (1951). *Proc. Mayo Clin.*, **26**, 361.
Wolbach, S. B. (1933). *Amer. J. Path.*, **9**, 689.
Wu, T. T. (1937). *Virchows Arch.*, **300**, 373.

Meeting in Geneva on May 19 to discuss birth control, the World Health Organization decided not to follow further the proposal put forward by the Norwegian delegate to study the "health aspects" of the world population problem (*New York Times*, May 20). This was because delegates from several predominantly Roman Catholic countries had said that action in this field would endanger the whole existence of W.H.O. Dr. Karl Evang had suggested they should look into the possibility of government propagation of birth-control methods in over-populated countries. The Belgian delegate put forward a counter-proposal forbidding any action of this sort. Had this been accepted it would have put a stop to the work already being done by W.H.O. in India and various other countries on family planning. The question was debated for two days, and then all the delegates agreed to drop the whole matter without a vote, in the interests of harmony. Secretariat officials said afterwards that they did not consider themselves bound in any way to stop advising governments on family planning as a result of this discussion. Only a formal decision by the Assembly could do this. In a letter to *The Times* on May 23, Lord Horder, commenting on the Roman Catholic threat of a mass walk-out in the event of acceptance of Norway's proposals, says that by their action they have possibly "prevented action which might have saved millions of lives." The problem of population, he writes, increases with every hour of every day and, without the knowledge of birth control, can be solved only by disease and other means involving much human suffering.

THE PREVENTION OF STREPTOMYCIN RESISTANCE BY COMBINED CHEMOTHERAPY

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The value of chemotherapy, combining streptomycin and P.A.S., in the treatment of certain forms of pulmonary tuberculosis was demonstrated in a Medical Research Council (1950) report of a controlled investigation. In particular it was shown that association of P.A.S. with streptomycin substantially reduced the risk of development of drug resistance. The daily dose of P.A.S. used was 20 g. of the sodium salt, a dose which produced gastro-intestinal discomfort in more than half the patients. It was decided to investigate whether smaller doses of P.A.S. would have the same effect on drug resistance: that investigation has been completed, and the results are reported here. The inquiry was planned and directed, as the previous trial, by a joint subcommittee of the Medical Research Council's Streptomycin in Tuberculosis Trials Committee and the British Tuberculosis Association's Research Committee, and the centres at which the work was carried out were the same as before.*

It was decided to have three concurrent groups, with the same type of disease as in the previous trial, and to use the same daily dose of streptomycin for all groups, but different doses of P.A.S. (5, 10, or 20 g.). The main analysis would concentrate on the results of streptomycin sensitivity tests. Since these would give a clear numerical differentiation, smaller groups were needed than for the previous trial, and the collection of cases, which had started in November, 1949, was stopped at the end of December, 1950, with 115 patients in the investigation.

*Members of the Joint Subcommittee: Sir Geoffrey Marshall (chairman), Professor R. Cruickshank, Dr. Marc Daniels, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. K. Perry, Dr. J. G. Scadding, Dr. W. E. Snell, and Dr. P. D'Arcy Hart (secretary).

Centres, clinicians, and pathologists collaborating:

Brompton Hospital, London.—Clinician: Dr. J. R. Bignall (working under the direction of the honorary staff of Brompton Hospital). Pathologists: Dr. J. W. Clegg, Dr. T. D. M. Martin.

Clare Hall County Hospital, Herts.—Clinician: Dr. T. A. W. Edwards. Pathologists: Dr. H. Loewenthal, Dr. R. F. Welch.

Colindale Hospital, London.—Clinicians: Dr. W. E. Snell, Dr. G. O'Malley, Dr. W. C. Harris. Pathologists: Dr. J. L. Hamilton-Paterson, Dr. E. D. Hoare.

Aintree Hospital (late Fazakerley Sanatorium), Liverpool.—Clinicians: Dr. O. F. Thomas, Dr. J. Hamilton Gifford. Pathologists: Professor A. W. Downie, Dr. C. A. St. Hill.

Harefield County Hospital, Middlesex.—Clinicians: Dr. L. E. Houghton, Dr. G. P. Maher-Loughnan, Dr. J. Sumner. Pathologist: Dr. E. Nassau.

King George V Sanatorium, Surrey.—Clinicians: Dr. J. V. Hurford, Dr. M. Francis. Pathologist: Dr. N. P. L. Wildy.

London Chest Hospital, London.—Clinician: Dr. L. J. Grant. Pathologist: Dr. W. I. Leslie.

London Hospital Annexe, Essex.—Clinicians: Dr. K. Perry, Dr. N. Lloyd Rusby, Dr. D. C. L. Beatty. Pathologist: Dr. F. C. O. Valentine.

Sully Hospital, Glamorgan.—Clinician: Dr. L. R. West. Pathologist: Dr. Ruth L. Milne.

Yardley Green Hospital, Birmingham.—Clinician: Dr. Hector J. T. Ross. Pathologist: Dr. B. R. Sandiford.

Dr. Marc Daniels, of the M.R.C. Tuberculosis Research Unit, was responsible for the co-ordination of the trial, and he also analysed the results and prepared the report for the Committee. Professor A. Bradford Hill was responsible for the statistical design of the trial. The radiological results were assessed by Dr. G. Simon.