

drome has attracted considerable attention, but most of this work has concerned patients seen because of rheumatic complaints.

This study surveys a group of patients with KCS as the index symptom attending a special clinic at Moorfields Hospital, and establishes the prevalence of rheumatoid arthritis and other connective tissue diseases, in comparison with a matched control group. 'Auto-immunological' activity was studied.

Of the 65 patients surveyed, 23 had rheumatoid arthritis, 24 had xerostomia or parotid swelling without evidence of other connective tissue disease, four had progressive systemic sclerosis or variants thereof, and in fourteen the KCS was the sole manifestation.

Autoantibodies were found in a remarkably high number of patients, especially antinuclear factor, comparable to series with more systemic involvement, but rheumatoid factor was less common. Immunoglobulin levels were considerably raised. Antibody against salivary gland duct epithelium was also found mainly in the rheumatoid subjects but was seemingly unrelated to overt parotid involvement.

Discussion

DR. A. K. THOULD (*Truro*) What thyroid disorders did you find in your patients with rheumatoid arthritis and Sjögren's syndrome?

DR. GUMPEL Ordinary uncomplicated goitre without thyrotoxicosis or myxoedema.

DR. A. K. THOULD (*Truro*) No evidence of a thyroiditis for instance?

DR. GUMPEL No. The results for thyroid antibodies as gauged by a thyroid microsomal antibody were not higher in these patients than in any of the others.

DR. W. W. BUCHANAN (*Glasgow*) I was particularly interested in the group of patients with KCS, because, as you say, no one has made a systematic study of these patients. From your observations it would appear that they have a mild degree of Sjögren's syndrome. Have you considered doing a labial mucosal biopsy on these patients, because this shows miniature Sjögren's syndrome in about 60 per cent. of patients with the fully expressed disease. It would be interesting to know whether patients with KCS alone had this lesion in their oral mucosa.

DR. GUMPEL There were a number of other investigations I should also have liked to do in the whole group, but because they are a fairly unusual population they are notably reluctant to submit to further medical attention or investigation. I propose, however, to investigate this group once again.

Ehlers-Danlos Syndrome. By P. BEIGHTON (*St. Thomas's Hospital*)

The Ehlers-Danlos syndrome is a genetically-determined disorder of connective tissue, characterized by hypermobile joints, hyperextensible skin, and a tendency for the skin to split on minor trauma with the formation of wide gaping scars. The condition is rare and about 300

cases have so far been recorded in the world literature.

During a recent survey in Southern England 100 cases have been examined and the following significant facts have emerged:

(1) The syndrome is probably composed of five separate entities which are clinically recognizable. The importance of these is that one of them is lethal, with a high incidence of sudden death, one is associated with many minor complications, and one is transmitted as an X-linked trait. The implication of this last fact is that this particular variety of the Ehlers-Danlos syndrome must be a completely separate condition.

(2) It has become apparent that musculoskeletal disorders occur generally in the Ehlers-Danlos syndrome. Among these are joint dislocations and subluxations, thoracic abnormality, and spinal deformity.

(3) Biochemical, haematological, chromosome, and genetic linkage investigations have been carried out.

Discussion

MR. A. P. BARABAS (*Postgraduate Medical School*) I should like to congratulate Dr. Beighton on this most thorough study of a large group of Ehlers-Danlos patients. In 1967 I examined 27 patients in the north of England with the same syndrome and it may be of interest to compare my findings with his. My classification basically agrees with that of Dr. Beighton. His 'gravis' group, the severely affected ones, I call the 'classical'. I have seen three families in his less severely affected 'mitis' group and they all had varicose veins. This may have happened by chance, but at the time I called the group the 'varicose' type. I have not seen any X-linked families, but I have observed one family which could be classified as 'benign hypermobile'. My main interest has been in the 'arterial' subjects which I think correspond to Dr. Beighton's 'ecchymotic' group. I think this is the most important group because in my series lethal complications occurred exclusively amongst the 'arterial' cases. I should like to ask Dr. Beighton, in view of the entirely different prognosis and also the different clinical and diagnostic picture, whether he would not agree to call the 'arterial' or 'ecchymotic' type a completely different disease? I think there would be practical advantages in this.

DR. BEIGHTON Yes, I think Mr. Barabas is quite right in this. Patients with the arterial or ecchymotic type of condition are clinically recognizable. They have thin, pale skin, with a very, very prominent venus plexus, their bleeding tendency is enormous, their scars tend to be darkly pigmented, and they are clinically very different, with a very high risk of the serious complications of dissected aorta, perforated gut, or ruptured arteries. Some time ago Mr. Barabas proposed (*Proc. roy. Soc. Med.* (1969), 62, 735) that this condition should be known as Sack's syndrome, as some years ago Sack described a 'status disvascularis', and I think this is a very reasonable suggestion. It must also be made perfectly clear that, although these lethal complications have a very high incidence in these clinically recognizable patients, those

with the major stigmata of the condition itself are also at some risk. By this I mean that, of my 100 patients, one with the major stigmata suffered a dissected aorta, one American girl had a perforation of the bowel, and at least one man ruptured a major artery. Serious complications are thus not confined to this one recognizable group, but their incidence is comparatively great while the risk in the other patients is small.

DR. V. WRIGHT (Leeds) This was an excellent presentation. We have looked at the Ehlers-Danlos syndrome from the point of view of hypermobility of the joints because we were interested in methods of measurement, and we have published work on the elastic and plastic stiffness of the joints, showing that there was a decreased elastic stiffness and an increased rate of stress relaxation. When we analysed the factors which produced these two things, the only common factor we could find was an alteration in the ground substance, not any alteration in the collagen nor in the wicker work. I wonder if you have any ideas about this or whether you think that the fundamental defect may lie not in the collagen and elastin, but in the ground substance?

DR. BEIGHTON I think that at this stage nobody has the faintest idea where the abnormality lies. Clearly, collagen is intimately related to the ground substance, and an abnormality of the ground substance could be reflected in this way in the collagen.

DR. K. T. RAJAN (Stoke Mandeville) Would you care to comment on the work of feeding a lysine-deficient diet to rodents? After they have been on a deficient diet for about 6 months these animals usually have impaired wound healing and laxity of the skin. There may thus be a deficiency of lysine which could be elucidated if one looked at the molecular level where there might be a defect in the lysine/proline linkage.

DR. BEIGHTON Much thought has been given to this possibility. Lysine is indeed involved in the formation of the cross-links in collagen, and animal fed on lysine-deficient diets do develop lax skin and fail to heal. Is the problem then one of lysine in the Ehlers-Danlos syndrome? At this stage, something like 5 per cent. of the collagen molecule has been sequenced, so that we do not know whether it is lysine that has been substituted. If there is a substitution, lysine seems the obvious answer, but there is more to it than this. The formation of the lysine cross-links is in a way catalysed by the monoamine oxidase enzymes, so again the question is, are we dealing with an enzyme problem? This enzyme works only in the presence of copper and again we have animal experiments: chickens fed on copper-free diets have developed the same stigmata, the skin becomes lax and the collagen falls apart. So again, is the problem one of copper metabolism, inhibiting monoamine oxidase, inhibiting lysine cross-links? Again, we do not know. Lysine links may well be involved, but the problem is, at what level?

DR. J. BALL (Manchester) Is it known whether there are quantitative changes in the collagen content of the undamaged skin of these patients?

DR. BEIGHTON Not that I am aware of.

MR. A. P. BARABAS (Postgraduate Medical School) I can answer this. We have compared the skin of one

patient with the Ehlers-Danlos syndrome with two matched controls, and there was no quantitative change in the total collagen or the acid- or salt-soluble collagen. It was in fact perfectly normal.

Reference

BARABAS, A. P. (1967) *Brit. med. J.*, 2, 612.

Atlanto-axial Instability in Rheumatoid Arthritis. By RODNEY SWEETNAM (Middlesex Hospital, London)

Atlanto-axial instability has been shown to be a relatively common complication of severe rheumatoid arthritis, but, our knowledge of its natural history is scanty and the indications for surgical treatment cannot yet be clearly defined.

It is possible that complications, even sudden death, may be more common than generally believed. Minor symptoms and signs may be confused with other more common features of rheumatoid arthritis, such as median nerve compression or the apparent weakness caused by painful inflamed joints. Death caused by damage to the cord or vertebral arteries may in some patients be wrongly attributed to other causes.

Surgical stabilization by posterior fusion is indicated in patients with severe unrelieved pain, in those with spinal cord or vertebral artery compression, and when there is increasing instability even in the absence of neurological signs. Fusion is not indicated in patients with minor degrees of subluxation without symptoms. Between these two groups, however, are very many for whom the indications for surgery remain debatable.

When stabilization of the atlanto-axial joint is indicated, posterior occipito-cervical fusion is the procedure of choice. A simple method is described in which no form of internal fixation is required. It has the merit of simplicity and reliability and may be performed even in the elderly, necessitating no more than 6 weeks in bed. Local atlanto-axial fusion is not recommended because sound fusion is achieved less often. Inclusion of the occiput virtually ensures success and reduces the total flexion/extension range of the whole cervical spine, usually by less than 30°. This loss of movement is often not noticed by the patient because the normal total range of such movement is about 140°. Loss of rotation is a greater disability, but this is a function of the atlanto-axial joint which must of course be fused.

Discussion

PROF. J. H. KELLGREN (Manchester) I was most impressed by your surgical technique, which seemed to be very, very simple. I am sure we need to know how often these things progress and how often they stabilize, but this is what we really do not know. We have certainly had a substantial number of patients over a 10-year period who have stabilized spontaneously; even some who had neurological defects have also regressed, either spontaneously or with the help of a very simple collar, applied not for immobilization but for prevention of gross trauma. We need a major long-term follow-up to know what the risks are. I suspect that many more cases stabilize than we think.