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 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 monooamine 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 monooamine 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**


**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.
In a post mortem study of twelve cases of atlanto-axial luxation, including five severe cases, there were three in which spontaneous ankylosis had occurred and these were all minor subluxations. It may be that spontaneous ankylosis is less likely in advanced cases.

PROF. J. H. KELLGREN (Manchester) In some of the cases I was quoting there was very large subluxation, a centimetre or more.

DR. E. B. D. HAMILTON (London) In the last 9 years at King's College Hospital we have seen 21 patients with severe subluxation of the cervical spine, but the subluxation did not occur at the atlanto-axial level in all of them. We operated on eleven because of cord compression and on two because of basilar artery insufficiency. Of the eight patients in the non-operated group, two went on to develop cord compression while under out-patient surveillance, but it was considered at this stage that operative treatment was contraindicated. One of the two had a subluxation at the atlanto-axial level and the other in the mid-cervical spine. Our experience would suggest, therefore, that the subluxation can progress while the patient is under observation and that the lesion does not remain static or regress in all cases.

MR. SWEETNAM It is a great unknown, is it not? We have all seen many patients with no signs or symptoms whatsoever in whom gross subluxation was found only by chance; one wonders whether perhaps there is a tendency for surgeons to operate too often, or alternatively not often enough. This is something we just do not know.

DR. J. A. MATHEWS (London) I agree with the main points in Mr. Sweetnam's lucid description of the indications and the contraindications for fusion of the upper cervical spine in rheumatoid arthritis. I have an impression, which is so far unsubstantiated, that the vascular and neurological sequelae of damage in this region are partly the result of the rapidity with which instability develops. This, I think, compounds the problem of deciding what to do with the patients in whom little or no atlanto-axial instability is demonstrable in a rheumatoid cervical spine. One cannot predict which of these patients will be subjected to some accidental trauma causing sudden, and sometimes lethal, damage, and I think this emphasizes your point that a follow-up study is badly needed.

DR. M. WILKINSON (Perth) I wonder what the patients think about this operation after they have had their necks fused? To say that they only lose 40° of flexion out of 140° is not necessarily true. At least half of them with gross subluxation have a C5-6 and possibly C6-7 disc lesion, so they already have a rigid section of their spine lower down; if you add a rigid section high up you are making them very stiff indeed. Of what little I have seen, they have not been happy patients after operation. Also I wonder if you are even relieving them of the risk of a whiplash injury? They retain only a tiny mobile portion of cervical spine which seems to be very vulnerable.

MR. SWEETNAM I take your point. It is clearly true that if you immobilize part of the spine you will throw a greater strain on the rest of it. If that remainder is already diseased, it will be more liable to damage. It so happens that the upper part of the cervical spine is more vulnerable than the lower and I think it is a question of choosing. I am not suggesting that patients are delighted to have any restriction of movement after operation, but in practice they complain that they can not turn the head fully but not of loss of flexion and extension. What does worry them is the loss of rotation; thus, concerning my argument about including the occiput in the fusion, the extra limitation of movement is not very important. Whether you fuse at all is important, for the patients are bound to lose something, but you must balance this against the advantages.

DR. J. T. SCOTT (London) A fact which is not often brought out in discussions of this problem is that emphasized by Isdale and his colleagues some years ago (Conlon, Isdale, and Rose, 1966), namely that these severe cervical subluxations are frequently associated with gross disease elsewhere. For example, there may be destructive lesions in the shoulders, hips, knees, and so on, and one is faced with the difficult decision whether or not to operate against a background of such severe generalized disease.

MR. SWEETNAM One of the great problems is that these patients are often very severely handicapped. It is surprising that they take occipito-cervical fusion so well; if a patient can tolerate lying in bed for 6 weeks, he can tolerate this.

DR. G. D. KERSLEY (Bath) I have a number of necks in bottles and also a number of patients who have been operated on and are very pleased with their operation. One of them goes back 20 years. But these were all cases that were producing definite neurological signs. I should like your view on those in which hypermobility and extreme pain are the main complaints and in which there is also involvement lower down the spine. Could you tell us more about the length of hospitalization with your technique?

MR. SWEETNAM To answer the last question first; it requires just 6 weeks, lying on a Stryker bed so that the patient can be turned. At first we always used skull calipers but now we seldom do so, because the graft unites so rapidly and so easily. After 6 weeks the patients are up in a collar. This is quite different from patients requiring posterior decompression, when fusion is not always obtained so easily. In rheumatoid arthritis such decompression is very rarely necessary. The first part of your question is more difficult to answer; I am here today seeking guidance simply because I do not know the answer myself. We all know what to do for patients with neurological signs; most of us would, I think, agree that fusion is indicated, particularly if there is also progressive or severe subluxation. The great difficulty, as you say, is what to do with the relatively minor cases, which are so common. We have all seen patients with no symptoms or signs, but with quite gross degrees of instability. Whether they should be fused or not cannot be definitely decided until a proper prospective study is carried out to see what proportion of them stabilize. Whether my suggestion that sudden death due to sub-
luxation is more common than we think is tenable. I
cannot say. The onus lies with those who treat their
patients without fusion to show that their method is as
safe as surgery.

DR. A. B. MYLES (Chertsey) Before advising a patient
with a symptomless subluxation and cord compression benefit
by this treatment. You have not told us your results. In
my experience, patients who have refused operation have done rather better than those who have had the
operation, and they have not, as expected, continued to
deteriorate. One or two have died subsequently with
other diseases and, although considerable subluxation has been found at autopsy, there is such laxity, that there
is no longer any compression on the cord, and it is not
clear that they are at risk.

MR. SWEETNAM This is marvellous. Here we have
someone who is presumably not going to submit any
more of his patients to surgery. Now it is held upon
him to provide us with a prospective study in 10 years’
time, and then we shall have the answer which we are
all seeking.

Reference
Dis., 25, 120.

Effect of a Fibrinolytic Agent (Arvin) on Wound Healing
and Collagen Formation. By P. J. L. HOLT, V. HOLLOWAY,
N. RAGHUPATI, and J. S. CALNAN (Departments of
Medicine and Experimental Surgery, Royal Postgraduate
Medical School)

A purified fraction of the venom of the Malayan pit
viper (trade name Arvin) is capable of producing complete
defibrinogenation. This is not associated with the
bleeding which occurs if heparin is used.

This drug was used to assess the effect of defibrino-
genation on wound healing and connective tissue forma-
tion. Standard wounds were produced on the backs of
rabbits and inert implants placed in the subcutaneous
tissue of the flanks. Almost complete defibrinogenation
was produced, plasma fibrinogen at all times being less
than 50 mg./100 ml. Similar unfibrinogenated rabbits were
used as controls, with a further group of animals in
which the plasma fibrinogen had been artificially
raised.

The wound strength and histology, the weight and
histology of new tissue formation around the implants,
and the histology of untouched skin were compared in
the three sets of animals.

Defibrinogenation produced impaired wound healing
and defective connective tissue formation. Alterations in
collagen and other skin structures in specimens of un-
touched skin were also found.

To elucidate the nature of these changes, in particular
the part played by Arvin directly and indirectly in de-
 fibrinogenation, were investigated in vitro and by the
use of further animal models.

Discussion

DR. D. L. GARDNER (Kennedy Institute) These subjects
are undoubtedly controversial, and I should like to ask
Dr. Holt how he preserved the tissues, the microscopic
preparations of which he illustrated and from the
appearance of which he deduced that ground substance
formation was diminished under Arvin treatment.

DR. HOLT They were all preserved in formal saline.

DR. D. L. GARDNER (Kennedy Institute) It is necessary
to be extremely careful in drawing conclusions on the
quantity of ground substance present in a tissue from
the study of microscopic preparations processed through
paraffin. Engfeldt and Hjertquist (1967, 1968) have
demonstrated by the use of 35SO4 that enormous losses of
matrix sulphated glycosaminoglycan quickly succeed
fixation in formaldehyde or glutaraldehyde followed by
postosmification and dehydration. In such preparations,
up to 70 per cent. of 35SO4 may be lost in the 4 hours
preceding embedding.

DR. HOLT I was aware of this, but it came out after
we had gone through the work, and I have said that we
are less certain of the ground substance until we have some
chemical measurements.

DR. H. MUIR (London) The histological changes pro-
duced by Arvin on the intact skin in adult animals
occurred within 7 days as judged from your last slides.
The effect would, therefore, appear to be on pre-formed
collagen, whereas the effect in wound healing is on newly-
formed collagen. Can you explain this?

DR. HOLT We tried a system of putting in an implant
at minus 4, minus 3, minus 2, and minus 1 week into the
control animal, and into some that were to be defibrino-
genated. From this we could find what an implant
which has been in for 4 weeks should weigh and so on.
What we hope to do, and this is very difficult, is (having
got our standards) to defibrinogenate one week after
the last implant is inserted and see what happens to it.
Suppose, for example, that an implant has been in for
1 week; will it gain weight normally, will it stay the
same weight, or will the weight fall? As I have said, we
had difficulty with our collagen estimations and extrac-
tions, but, judging the weight alone, we think it is follow-
ing a straight line; in other words, no new collagen is
being laid down. This work is very difficult because
there are such wide variations.

DR. H. MUIR (London) Has Arvin any effect on collagen
in vitro in the test tube in the absence of fibrinogen?
Does Arvin have any direct effect on soluble collagen?

DR. HOLT No. What we have done is add Arvin by
itself, Arvin with serum (plasma is of course instantly
cloaked), in thin preparations in the test tube, and to
compare this with the effect of trypsin, collagenase,
and papain. In these circumstances we have found no effect
of Arvin in the test tube and we have used various pHs
and molarities. The trypsin, collagenase, and papain all
affected the tissues.

DR. R. GRAHAME (London) How did Dr. Holt measure
the tensile strength and did he estimate the strength of
healthy skin of the animal as well as that of the scar
tissue?

DR. HOLT Measurement of healthy skin is very difficult
and needs a large machine. We had thought about this.
Atlantic-axial instability in rheumatoid arthritis.

R Sweetnam

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