estimated before and after 14 days of the following treatments: indomethacin 200 mg daily; aspirin 3 g daily; phenylbutazone 300 mg daily; and ascorbic acid 500 mg daily. At least eight patients were allocated to each group. No change in gastrin levels was detected. In addition, in short-term studies of 1 hr duration no change in immunoreactive gastrin levels were found after the exhibition of indomethacin 75 mg and tetracosactrin depot. However, it has been shown that canbenoxolone, a powerful anti-inflammatory agent, in a dose of 200 mg daily for 14 days in sixteen patients with rheumatoid arthritis produced no change in serum immunoreactive gastrin (160-3 ± 55-4 pg/ml to 168-1 ± 55-9 pg/ml), but a rise in serum immunoreactive secretin (63.3 ± 13.68 pg/ml to 91.3 ± 10-9 pg/ml; t = 1.82; P < 0.05).

To determine whether the rise in immunoreactive serum gastrin levels in rheumatoid arthritis was due to chronic inflammation an experiment was carried out in twenty-three male Sprague-Dawley rats. Fasting serum immunoreactive gastrin levels were estimated before and 14 days after the induction of adjuvant arthritis. There was a significant increase in the levels (211 8 ± 41 1 pg/ml to 478 7 ± 72-7 pg/ml; t = 3.182; P < 0.05). Time-course studies to date indicate that this effect is maximal at 7 days.

From these studies it is concluded that there is a relationship between hypergastrinaemia and certain forms of chronic inflammation. The results of the drug studies suggest the possibility of screening for anti-inflammatory compounds by means of radioimmunoassay of gastrin and secretin, to find active compounds which also affect the levels of these hormones. In this way iatrogenic gastric complications may be avoided.

Discussion

DR. T. SCOTT (London) I wonder if you could enlighten us upon a point which applies to radioimmunoassay in general. As you say there are at least two molecular forms of gastrin and we are told that there are now in fact considerably more—about ten I believe—depending upon molecular size, sulphation, and so on; so I would like to ask you which molecule you are estimating and its relation to biological activity?

DR. ROONEY The assay we are using measures the heptadecapeptide which is considered the natural hormone, as well as what have been described as big and big-big gastrin. We have no information as yet as to which, if any, of these we are measuring in the rheumatoid subjects.

DR. J. KACAKI (Holland) Have you seen any difference in plasma gastrin within your group of patients with rheumatoid arthritis and between those with gastric ulcers and those without gastric ulcers?

DR. ROONEY In the group that we studied originally in detail only seven had any complaint of dyspepsia and of these two were shown to have duodenal ulcers, two had gastro-oesophageal reflex, and in the remainder we could find no gastrointestinal pathology.

DR. J. A. BOYLE (Glasgow) Have you considered the possibility that gastrin activity might be artifactual and have you actually tried to assay biological activity?

DR. ROONEY The Oxford Dictionary defines an artifact as an unnatural product; this is not an unnatural product, this is something which is present in the plasma of rheumatoid subjects. The nature of it is something which we have been investigating. One of the difficulties is that biological assay of gastrin is difficult and most systems require quantities in ng rather than quantities in pg, which we are measuring in this assay.

DR. G. S. PANAYI (London) This is a very interesting observation which you have presented. We have also just completed a study at Guy's with Dr. A. Unger in the Department of Medicine (Unger, Panayi, and Lessof, 1974) on another product from the gut, namely carcino-embryonic antigen. We have shown that there is a markedly raised level of the antigen in the plasma of rheumatoid patients and not in other joint inflammatory diseases such as psoriasis and ankylosing spondylitis. We don't know what this means at the moment, or whether it correlates with disease activity, but it does seem to indicate that there might be some kind of relationship between the gut and the joint, but more importantly that there may be some objective laboratory method for measuring either disease activity or monitoring drug treatment.

PROF. E. G. L. BYWATERS (Taplow) How did the authors begin to investigate or come across this association?

DR. ROONEY The relationship between rheumatoid arthritis and the gastrointestinal tract is a close one, particularly through the relationship of complications of anti-inflammatory drug therapy, and it is fortunate for us that Professor Buchanan's brother happens to be measuring immunoreactive gastrin in Belfast.

Reference


Antagonism of the Histamine Response in the Synovial Micrcirculation. By D. M. GREENNAN, P. J. ROONEY, E. GILBERTSON, and W. CARSON DICK (Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow, and Department of Veterinary Surgery, Glasgow University Veterinary Hospital, Bearsden, Glasgow)

The study was designed to investigate the effects of H2 receptor antagonist metiamide on the histamine vascular response in the synovial microcirculation. The half-life (T½ mins) of the clearance rate of xenon (133Xe) from diarthrodial joints provides an indirect measure of synovial perfusion (Dick and others, 1970) and this method has been used in the past to show the presence of adrenergic and cholinergic receptors in the synovial microvasculature (Dick, 1972). In the present study the xenon clearance rate was shown to be consistently increased by histamine and unaffected by various concentrations of the H2 receptor antagonist metiamide alone. The H1 antagonist mepyramine did not block the effects of histamine up to a dose ratio of 1,000 (Met:H), but metiamide produced a dose-related effect with consistent abolition of histamine response at concentration ratios (Met:H) of 500:1 and 1,000:1, variable response in a
dose ratio of 200:1, and a pronounced histamine response in a dose ratio less than 200:1. These results reflect the presence in the synovial microvasculature of $H_2$ receptors which may be involved in the control of peripheral blood vessels.

**Discussion**

**DR. M. I. V. JAYSON** (Bristol) With respect to the particular experiments in which you studied the effects of histamine after metiamide, in several of them the half-life of the xenon within the joint was considerably lower than normal before injection of the histamine. In these particular cases, may it not be a bit much to expect a further shortening of the half-life and increased clearance by the histamine so that the lack of histamine response at these concentration ratios of 500:1 and 1,000:1 may not indicate a specific blocking effect?

**DR. GRENAN** In the first slide we tried to show the effects of metiamide alone on xenon clearance and we thought there was no significant response to metiamide given alone. If you are referring to the fact that at the 1,000 $\mu$g dose of metiamide the mean value of the baseline clearances pre-histamine appears slower, then I must point out that at this supra-blocking dose we have only done 3 experiments which are weighted by one disproportionately slow clearance of 150. There is a considerable individual variation in the xenon clearance from individual joints but it has been shown that the method does provide acceptable repeatability on the same joint with repeated xenon clearances.

**DR. A. BENNETT** (London) Your results show that $H_2$ receptors are present only if the antagonism is selective. Did you determine its effect on responses to other substances such as isoprenaline?

**DR. GRENAN** Yes. We have shown that as regards $\alpha$ and $\beta$ sympathetic stimulation in the doses of sympathetic agents that we have used there has been no cross-over antagonism.

**References**


**Tissue Gold Levels After Chryotherapy.** By R. GRAHAME, R. BILLINGS, M. LAURENCE, V. MARKS, and P. J. WOOD (Guy's Arthritis Research Unit, and Department of Biochemistry, University of Surrey) *Annals*, 33, 536.

**A Biographical Sketch of George Frederick Still.** By E. B. D. HAMILTON, *Kings College Hospital, London*

**HL-A Antigen W27 in Juvenile Chronic Polyarthritis.** By J. EDMONDS, A. METZGER, P. TERASAKI, R. BLUESTONE, B. ANSELL, and E. G. L. BYWATERS (M.R.C. Rheumatism Unit Tapol, and University of California, Los Angeles)

The long-term follow-up of children suffering from chronic polyarthritis suggests that while the majority remain seronegative with the disease tending to remit, some develop ankylosing spondylitis and others a saccroiliitis consistent with ankylosing spondylitis; among those with saccroiliitis and ankylosing spondylitis, acute iridocyclitis is not uncommon. A small group have pauciarticular involvement with chronic iridocyclitis and a positive antinuclear factor; a few develop psoriasis and some have a pattern of illness similar to adult rheumatoid arthritis.

Ninety per cent. of Caucasian patients with ankylosing spondylitis have been shown to be of the tissue type HL-A W27 compared with 8% of controls (P = 0.0001) (Schlosstein and others, 1973), thus suggesting this tissue type is a marker for ankylosing spondylitis. We have, therefore, investigated the HL-A phenotype frequencies in forty-nine patients with juvenile chronic polyarthritis who were attending our follow-up clinic. The shortest duration of follow-up was eight years and the longest thirty-three years, with the majority just over fifteen years. All showed some clinical residua; when no sacroiliac film was available, a pelvic film was obtained at the same time as the blood sample. In seven, a diagnosis of ankylosing spondylitis as a sequel to their Still's disease has been made, six of these were of the HL-A W 27 type; the eight who had saccroiliitis of ankylosing spondylitis type, irrespective of the presence or absence of activity of their peripheral arthritis, all belonged to the HL-A W27 group. Of the twenty-one seronegative Still's, three belonged to this phenotype, but their present pelvic films show no evidence of saccroiliitis. Eleven had seropositive juvenile rheumatoid arthritis; none of these had the HL-A W 27 antigen. There was no case of psoriasis in this study (Brewerton and others, 1973).

It therefore appears that the presence of HL-A W27 in juveniles suffering from polyarthritis may be a valuable marker in characterizing the type of disease present in a particular patient. It should certainly alert the clinician to the high probability of the later development of saccroiliitis and probably also of spondylitis.

**Discussion**

**DR. D. A. BREWERTON** (London) The third group with peripheral arthropathy and no saccroiliitis is going to be a problem in classification. It has its equivalent in adults. As yet, we do not know how many adults with HL-A 27 have seronegative peripheral arthropathy, but the rigid definition that saccroiliitis must be present to diagnose ankylosing spondylitis-like disease is no longer tenable. At the Royal National Orthopaedic Hospital it is a regular problem to us that orthopaedic surgeons see children, particularly boys in the 8-15 age range, with mild conditions such as tenosynovitis or a swollen ankle with a normal ESR who later develop ankylosing spondylitis. In this group it is of considerable diagnostic help to determine the HL-A antigens.

**DR. EDMONDS** It does seem that HL-A cannot be used as a specific marker for the presence of saccroiliitis or spondylitis.

**DR. R. M. MASON** (London) Did you survey your patients for urethritis?

**DR. EDMONDS** No.

**References**
