DR. E. GLICK (London) I think we have to be careful about interpretation. This was not a trial of bed rest, it was a trial of hospitalization, as the wording of the summary makes clear. All the outpatients had a minimum of 8 hrs bed rest, so you were comparing 8 and 13 hrs which are not very different. It is hospitalization and avoidance of a lot of the minor trauma that goes with looking after houses and so on, that you have been testing and not bed rest alone.

DR. LEE Yes, it is hospital inpatient treatment versus outpatient treatment. I think hospital inpatient treatment involves more than bed rest because the patient is actually removed from the burden of domestic and business worries as well.

References

A Double-blind Comparative Trial of Cyclophosphamide and Gold in Rheumatoid Arthritis. By J. M. GUMPPEL, A. HALL, and B. ANSELL (M.R.C. Rheumatism Unit, Canadian Red Cross Memorial Hospital, Taplow)

A comparative study of gold and cyclophosphamide was started in this unit in December 1969. Sixty-seven patients with rheumatoid arthritis whose disease activity was not controlled by conventional therapy and who would, in the ordinary course of events, have been treated with gold have entered the study. All had completed their families, and were willing to enter a trial of this nature. By random selection the patient received either cyclophosphamide and dummy gold injections, or gold and dummy cyclophosphamide. The therapy was controlled by one physician, while the clinical state of the patient was regularly assessed by a second physician without knowledge of the active drug or of any side effects that had occurred. This report is on the first year of treatment of fifty patients.

There was statistically significant improvement in functional state in patients on gold and on cyclophosphamide. The results for decrease of joint pain, increase in grip strengths, and improvement in walking time were significant for the patients on cyclophosphamide but not for those on gold. The ESR improved in both groups, the significance being greater (P = 0.001) with gold than with cyclophosphamide. Side effects were more common with cyclophosphamide but no patient was withdrawn from cyclophosphamide because of drug-related side effects, whereas three patients were withdrawn from gold therapy because of severe gold rash.

Discussion
DR. H. L. F. CURREY (London) Can you correlate the dose of cyclophosphamide with the response of the patients? Two trials have shown what appears to be a threshold effect and I wonder whether you have looked for this? Secondly, comparing your results with ours from The London Hospital, I am impressed that your results with cyclophosphamide are better than ours, from the point of view of both toxicity and clinical response, and I think the reason for this is that you tailored the dose, whereas we had to use a fixed dose.

DR. GUMPPEL A special feature in the design of this study and the reason for having an independent assessor was that it gave us this freedom to tailor the dose to suit the patient. This was very important, and we think that if we had used a fixed dose as you mention in your study, we would have had more toxicity.

DR. J. KACAKI (Holland) Have you studied some parameters of cell mediated immunity in your group of patients treated with cyclophosphamide?

DR. GUMPPEL Initially we studied at the beginning of treatment and after 3 months, but abandoned this because of our concern about the reproducibility of the results and especially with staff shortages and changes.

DR. P. A. BACON (Bath) I think your study very nicely confirmed that cyclophosphamide is one of the most effective drugs for rheumatoid arthritis around at present and that the chief problem is controlling the toxicity. I have recently been giving a large dose, 2 mg/kg, but as an intermittent dose, I week on and 1 week off or variants of this regimen. My initial impression is that one can get a good effect with this sort of intermittent therapy and I think toxicity may be less. Have you any experience of this sort of regimen?

DR. GUMPPEL No, but the regimen you mention has many theoretical attractions.

DR. C. BARNES (London) Were there any radiographic differences comparing films taken at the beginning and end of the trial?

DR. GUMPPEL Yes, in many patients we have seen healing of erosions both on gold and on cyclophosphamide. We have spent considerable amounts of time looking at the radiographs, and have just recently worked out a system that will allow us to produce a meaningful score to compare before and after treatment.

On the Relationship Between Inflammatory Joint Disease and the Foregut Hormones, Gastrin and Secretin. By P. J. ROONEY, J. MILLAR, J. R. HAYES, K. D. BUCHANAN, and W. C. DICK (The Centre for Rheumatic Diseases, University Department of Medicine, Royal Infirmary, Glasgow; University Department of Medicine, Queen's University of Belfast)

Serum immunoreactive gastrin levels have been found to be raised in approximately one-third of patients with rheumatoid arthritis. No increase in serum gastrin levels has been noted in eight patients with psoriatic arthritis, twenty-three patients with systemic lupus erythematosus, seventeen patients with ankylosing spondylitis, and twenty-five patients with osteoarthritis. In addition, no rise in immunoreactive gastrin was observed in sixteen patients with active pulmonary tuberculosis and ten patients with recent myocardial infarction (within 48 hrs).

Studies have been conducted in patients with rheumatoid arthritis in which fasting immunoreactive gastrin was
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 carbenoxolone, 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±35 55-4 pg/ml to 168±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 (218±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. J. 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 reflux, 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 Microcirculation. 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 diarthroidal 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 H3 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
Proceedings: On the relationship between inflammatory joint disease and the foregut hormones, gastrin and secretin.

P J Rooney, J Millar, J R Hayes, K D Buchanan and W C Dick

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