E.O.R.T.C., Breast Cancer Group (1973). European Journal of Cancer. To be

B.O.R. T.C., Breast Cancer Group (1973). European Journal of Cancer. To be published.
Folca, P. J., Glascock, R. F., and Irvine, W. T. (1961). Lancet, 2, 796.
G.E.C.A. (1967). European Journal of Cancer, 2, 201.
Jensen, E. V., De Sombre, E. R., and Jungblut, P. W. (1967). Endogenous Factors Influencing Host-Tumor Balance, ed. R. W. Wissler, T. L. Dao, and S. Wood, jun. Chicago, University of Chicago Press.
Jensen, E. V., Block, G. E., Smith, S., Kyser, K., and De Sombre, E. R. (1972). Estrogen Target Tissues and Neoplasia, p. 23. Chicago, University of Chicago Press.

King, R. J. B., Cowan, D. M., and Inman, D. R. (1965). Journal of Endo-

King, R. J. B., Cowan, D. M., and Inman, D. R. (1903). Journal of Enwacrinology, 32, 83.
King, R. J. B., Gordon, J., Cowan, D. M., and Inman, D. R. (1966). Journal of Endocrinology, 36, 139.
Korsten, C. B., and Persiin, J. P. (1972). Zeitschrift fur klinische Chemie und klinische Biochemie, 10, 502.
Maass, H., Engel, B., Hohmeister, H., Lehmann, F., and Trams, G. (1972). American Journal of Obstetrics and Gynecology, 113, 377.
Trams, G., and Maass, H. (1969). In Fortschritte der Krebsforschung, ed. C. G. Schmidt and O. Wetter, p. 9. Stuttgart, Schattauer.

## PRELIMINARY COMMUNICATIONS

# Hypergastrinaemia in Rheumatoid Arthritis: Disease or Iatrogenesis

P. J. ROONEY, J. VINCE, A. C. KENNEDY, J. WEBB, P. LEE, W. C. DICK, K. D. BUCHANAN, J. R. HAYES, JOY ARDILL, F. O'CONNOR

British Medical Fournal, 1973, 2, 752-753

#### Introduction

The interplay of rheumatoid arthritis, peptic ulceration, and anti-inflammatory drug therapy remains highly complex and poorly understood. Recent advances in the technology of the measurement of intestinal hormones provide a new approach to the problem. We report an unexpectedly high incidence of markedly raised plasma gastrin levels in rheumatoid arthritis.

## Materials and Methods

Fifty patients with classical or definite rheumatoid arthritis (Ropes et al., 1959) were studied. The mean age ( $\pm$  S.E. of mean) was 54 ± 1.58 years. A group of 100 control subjects, mean age 55  $\pm$  2 years without known rheumatoid arthritis, pernicious anaemia, or gastrointestinal disease, were also studied. The clinical features of the patients with rheumatoid arthritis are summarized in the table. These patients comprised consecutive admissions to the Centre for Rheumatic Diseases over a period of one month.

The following clinical and laboratory data were recorded in all patients with rheumatoid arthritis in addition to age and sex: clinical articular index of joint tenderness (Ritchie et al., 1968),

Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow G4 0SF

P. J. ROONEY, M.B., M.R.C.P., Senior Registrar
J. D. VINCE, M.B., CH.B., Senior House Officer (Present address: University
Department of Child Health, Glossop Terrace Maternity Hospital

Cardiff)
A. C. KENNEDY, M.B., M.R.C.P., Research Fellow
J. WEBB, M.B., M.R.A.C.P., Lecturer
P. LEE, M.B., M.R.A.C.P., Senior Registrar
W. C. DICK, M.B., M.R.C.P., Consultant Physician

## Department of Medicine, Queen's University, Belfast BT7 1NN

K. D. BUCHANAN, M.D., F.R.C.P., Senior Lecturer
J. R. HAYES, B.SC., M.R.C.P., Research Fellow (in receipt of a grant from the Royal Victoria Hospital, Belfast)
JOY ARDILL, B.SC., Research Fellow
F. O'CONNOR, M.B., M.R.C.P., Registrar in Medicine

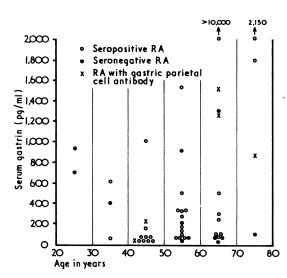
presence or absence of subcutaneous nodules; haemoglobin concentration; white cell count; erythrocyte sedimentation rate (E.S.R.); plasma proteins; titre of rheumatoid and antinuclear factors; gastric parietal cell autoantibody; and joint x-ray appearances. A record of past and present drug therapy was made and each patient was carefully questioned regarding dyspepsia. Those with a history of dyspepsia had a barium-meal examination.

The plasma gastrin was measured using a sensitive and specific radioimmunoassay. The assay uses antibody raised in rabbits to synthetic human gastrin.

Labelled hormone is prepared using a modification of the chloramine-T method of Hunter and Greenwood (1962) and separation of free hormone from that bound to antibody is achieved by treatment of the assay incubate with dextran-coated charcoal (Buchanan and McCarroll, 1971). Precision is greatest below 600 pg/ml and the sensitivity of the assay—that is, the lowest concentration of gastrin which can be differentiated from zero—is 10 pg/ml. Cross-reaction with cholecystokinin and pancreozymin is minimal, and preliminary studies show that the antibody recognizes not only the heptadecapeptide but also the "big gastrin" described by Yalow and Berson (1971).

## Results

The clinical features and laboratory indices in the rheumatoid arthritis patients are summarized in the table, and the fasting plasma gastrin levels in these patients are shown in the chart. The mean (± S.E. of mean) fasting plasma gastrin level of



Fasting plasma gastrin levels in patients with rheumatoid

Clinical Data on 50 Patients with Rheumatoid Arthritis

Sex			Age (Mean ± S.E.)	Sero- positive	Sero- negative	Sub- cutaneous Nodules	Kerato- conjuncti- vitis Sicca	Dyspepsia	Gastric Parietal Cell Antibody	Haemo- globin	E.S.R.	Articular Index	Blood Urea	Blood Sugar
										Range (and Mean ± S.E. of Mean)				
All patients	••	••	54·4 ± 1·58	40 (80%)	11 (22%)	11 (22%)	10 (20%)	7 (14%) (Barium	5 (10%)	8·3-16·9 (12·3	5-10 (52·4	2-62 (21·9	18-250 (39·9	48-113 (75-8
35 F. (70%)	• •		56·7 ± 1·7					neg. 1, duodenal ulcer 2,		± 2·4)	± 3·9)	± 2·2)	± 4·6)	± 3·96)
15 M. (30%)	••	••	49·7 ± 3·2					hiatus hernia 4)						

 $171 \pm 38$  pg/ml was significantly greater (P <0.005) than the mean fasting gastrin level in control subjects of  $56 \pm 8$  pg/ml. Plasma gastrin values were converted to logarithms before statistical analyses in order to normalize the distribution of values. In eight patients with rheumatoid arthritis the plasma gastrin level was greater than 1,000 pg/ml. In five patients with rheumatoid arthritis gastric parietal cell antibodies were found.

## Discussion

Raised gastrin levels have been described in patients with Zollinger-Ellison syndrome (Yalow and Berson, 1971) and in patients with pernicious anaemia or chronic atrophic gastritis (McGuigan and Trudeau, 1970 a). Acid secretory studies were not performed on the patients in the present study. Nevertheless, it is of interest that in only five patients were gastric parietal cell antibodies found. Of these, one had a normal gastrin level and only two had levels greater than 1,000 pg/ml. Hence, while this does not exclude chronic atrophic gastritis as a cause of the hypergastrinaemia, it makes it seem unlikely (Irvine et al., 1962). Plasma gastrin levels tend to rise with age (McGuigan and Trudeau, 1970 b) but in the control subjects and in the patients with rheumatoid arthritis the age distribution is similar. No obvious relation was found between gastrin levels and the severity of the arthritis as judged by raised E.S.R., a high articular index of joint tenderness, or the presence of anaemia.

Particular attention was paid to the possibility that drug therapy influenced the plasma gastrin levels. While this cannot be excluded, many patients being on several different drugs, no particular drug emerged as the likely aetiological agent. It is of course possible that this is a property of the anti-inflammatory drugs as a group, and this is under review. It is conceivable that the presence of rheumatoid factor in the serum of patients with rheumatoid arthritis could interfere with antibody binding in the gastrin assay. Raised gastrin levels, however, were found in both seronegative and seropositive patients (chart) and a normal plasma gastrin was found in 21 patients with seropositive arthritis of whom one had a titre greater than 1/256.

Dilutional studies showed that the immunoreactive material measured was immunologically identical to gastrin, and while this study is clearly limited and several questions remain unanswered, the finding of raised gastrin levels in patients with rheumatoid arthritis demands further study. If is of interest that of seven patients who complained of dyspepsia only one had a raised gastrin level.

Requests for reprints should be addressed to Dr. P. J. Rooney, Centre for Rheumatic Diseases, 35 Baird Street, Glasgow G4 0EH.

## References

Buchanan, K. D., and McCarroll, A. M. (1971). In Radioimmumoassay Methods, ed. K. E. Kirkham and W. M. Hunter, p. 136. London, Churchill Livingstone.
Ganguli, P. C., Cullen, D. R., and Irvine, W. J. (1971). Lancet, 1, 155.
Hunter, W. M., and Greenwood, F. C. (1962). Nature, 194, 495.
Irvine, W. J., Davies, S. H., Delamore, J. W., and Wynn-Williams, A. (1962). British Medical Journal, 2, 454.
McGuigan, J. E., and Trudeau, W. L. (1970 a). New England Journal of Medicine, 282, 358.
McGuigan, J. R., and Trudeau, W. L. (1970 b). Gastroenterology, 59, 6.
Ritchie, D. M., et al. (1968). Quarterly Journal of Medicine, 37, 393.
Ropes, M. W., Bennet, G. A., Cobb, J., Jacob, R., and Jessar, R. A. (1959). Annals of the Rheumatic Diseases, 18, 49.
Yalow, R. S., and Berson, S. A. (1970). Gastroenterology, 58, 609.
Yalow, R. S., and Berson, S. A. (1971). Gastroenterology, 60, 215.