Hypochlorhydria and hypergastrinaemia in rheumatoid arthritis

T. J. DE WITTE, P. J. GEERDINK, C. B. LAMERS,
A. M. BOERBOOMS, AND J. K. VAN DER KORST¹

From the Department of Medicine, University Hospital, Nijmegen, The Netherlands

SUMMARY In order to evaluate the incidence and aetiology of hypergastrinaemia 53 patients with seropositive rheumatoid arthritis were examined for gastric acid secretion, fasting serum gastrin concentration, circulating parietal cell antibodies, and some parameters of the activity of inflammation of rheumatoid arthritis. The basal and maximum acid output was found to be subnormal in this group ($P < 0.01$), and in 11 of these patients (23%) the fasting serum gastrin levels were raised ($P < 0.05$). This hypergastrinaemia correlated strongly with maximum acid output. Only in cases of achlorhydria or hypochlorhydria (maximum acid output less than 2 mmol/l) was the serum gastrin level markedly raised. Two out of 5 patients with achlorhydria were found to have circulating parietal cell antibodies, and 1 had decreased absorption of vitamin B₁₂. No relationship was found between serum gastrin and duration or activity of rheumatoid arthritis; nor was there a relationship between basal serum gastrin and the various antirheumatic drugs administered.

Rooney *et al.* (1973a, 1973b) have demonstrated a high incidence of hypergastrinaemia in patients with rheumatoid arthritis (RA). But the cause of this phenomenon was not established. The inflammatory activity, the duration of the rheumatoid arthritis, and the gastric acid secretion were found to be unrelated to serum gastrin levels, nor did the presence of rheumatoid factor in serum influence the serum gastrin levels (Rooney *et al.*, 1976a, 1976b). We have therefore investigated the incidence and the possible causes of the increased fasting serum gastrin levels in patients with rheumatoid arthritis.

Patients and methods

Fifty-three patients were included in this study. 28 females and 25 males with a mean age of 55 years (range 17-74 years). All patients met the criteria of the American Rheumatism Association for the diagnosis of classical or definite rheumatoid arthritis (Ropes *et al.*, 1959). The age of males and females was not statistically different. Mean duration of the RA was 9 years (range 1-35 years). All

patients had a positive haemagglutination reaction with sensitised sheep cells, according to the technique of Svartz-Schlossman, and none had undergone previous upper abdominal surgical operations.

Eight patients were not taking any antirheumatic medications; the others were receiving indomethacin, gold, or corticosteroids, or a combination of these drugs. The activity of joint inflammation was assessed by means of an articular index; tenderness, warmth, and swelling of all joints were measured by the same investigator.

A matched control group consisted of 28 persons, 14 males and 14 females, with a mean age of 55 years (range 36-75 years) without any sign of rheumatoid arthritis, or upper abdominal complaints.

Fasting serum gastrin was measured by a radioimmunoassay technique (Stadil and Rehfeld, 1973; Lamers and van Tongeren, 1977). The gastrin antiserum was raised in a rabbit against synthetic human gastrin I containing residues 2 through 17 (SHG 2-17, Imperial Chemical Industries Ltd) conjugated to bovine albumin. Gastrin components I, II (gastrin-34), III (gastrin-17), and IV (gastrin-13) could be demonstrated by using this antibody. The antibody reacted with sulphated and non-sulphated forms of gastrins I, II, and III with almost equimolar potency (Rehfeld *et al.*, 1975).

Gastric contents were collected according to the

Accepted for publication 10 April 1978

¹ Present address: Amsterdam Centre for Rheumatic Diseases, Dr Jan van Breemenstraat, Amsterdam-W 1056 AB, The Netherlands. Correspondence to Professor Dr J. K. van der Korst.

method of Hector (1968); the correct position of the orogastric tube in the stomach was checked by the water recovery test (Hassan, and Hobsley 1970). Pentagastrin in a dose of 6 µg per kg body weight was used for maximum stimulation of acid secretion. The gastric acid concentration was determined by titration of gastric juice with 0.1 N NaOH up to pH of 7.0. The basal acid output (BAO) during 1 hour, the maximum acid concentration (MAC) and the maximum acid output (MAO) during 1 hour were calculated.

The presence of circulating antibodies to parietal cells and intrinsic factor was measured according to the method of Taylor *et al.* (1962). Other immunological investigations performed on all patients were the sheep cell agglutination test, latex fixation reaction, antinuclear antibody test, and antiperinuclear antibody test (Nienhuis and Mandema, 1963). The following parameters of inflammatory activity were recorded: erythrocyte sedimentation rate (ESR), haemoglobin, and protein electrophoresis.

Statistical analyses were carried out by the Wilcoxon test for unpaired data. Regression analyses were done by the method of least squares.

Results

In 11 out of the 53 patients investigated fasting serum gastrin levels were raised, while none were raised in the 28 matched controls. The serum gastrin level of the whole group, 158 pg/ml (range 44–790 pg/ml), was significantly ($P < 0.05$) higher than in the matched control group, 67 pg/ml (range 43–97 pg/ml). As shown in Table 1, the basal gastric acid output, maximum acid output, and maximum acid concentration were significantly ($P < 0.01$) lower than in a group of 20 healthy persons. This population was subdivided into 5 different groups in accordance with the MAO, namely, total achlorhydria (group A); severe hypochlorhydria, MAO 0–2 mmol/h (group B); mild hypochlorhydria, MAO 2–6 mmol/h (group C); moderate hypochlorhydria,

Fig. 1 Correlation between fasting serum gastrin concentrations and maximum acid output in patients with seropositive RA. The mean for each group is shown as a solid line. Gastrin has been plotted on a logarithmic scale.

MAO 6–10 mmol/h (group D); and MAO more than 10 mmol/h (group E) (Fig. 1).

Markedly increased serum gastrin concentrations were found almost exclusively in patients with achlorhydria (group A) or severe hypochlorhydria (group B). These patients had significantly ($P < 0.02$) higher serum gastrin levels than patients in groups C, D, and E. Group A showed a weak tendency for higher gastrin levels than group B ($P = 0.1$). Two out of 5 patients with achlorhydria had parietal cell antibodies, and none had demonstrable antibodies against intrinsic factor. Only 1 patient showed an impaired absorption of vitamin B₁₂ (2.3% excretion of labelled vitamin B₁₂ in 48-hours urine; normal more than 15% in 48-hours), but this patient had no evidence of pernicious anaemia. None of the other patients had demonstrable circulating parietal cell or intrinsic factor antibodies.

In the RA patients with MAO more than 2 mmol/h there was no significant correlation between BAO and serum gastrin ($r = 0.22$) and between MAO and serum gastrin ($r = 0.03$). Furthermore, we found no correlation between the serum gastrin level and the age of the patients, duration of the rheumatoid arthritis, articular joint index, subcutaneous nodules, ESR, haemoglobin, antiperinuclear antibodies, and antinuclear antibodies. As shown in Fig. 2, no relation was found between serum gastrin levels and the various antirheumatic drugs used.

Table 1 Gastric acid secretion in patients with rheumatoid arthritis and in healthy controls

	Patients (n = 53)		Controls (n = 20)		P
	Mean	Range	Mean	Range	
Basal acid output (mmol/h)	1.2	0–11.4	2.3	0–9.7	<0.01
Maximum acid output (mmol/h)	10.4	0–29.4	23.3	6.5–50.3	<0.01
Maximum acid concentration (mmol/l)	83	0–148	113	74–143	<0.01

Fig. 2 Fasting serum gastrin levels in patients receiving various antirheumatic drugs. Patients with achlorhydria are represented by open circles and those with severe hypochlorhydria (MAO ≤ 2 mmol/h) by crosses. The normal range, expressed as mean $\pm$ 2 SD, is indicated.

Discussion

In a group of 53 patients with seropositive, definite or classical, rheumatoid arthritis a high frequency of hypergastrinaemia (23%) has been established. This is in accordance with the findings of Rooney *et al.* (1973a, 1973b, 1976a, 1976b). Whereas these authors found normal gastric acid output in almost all of their 16 RA patients with hypergastrinaemia, according to our data this hypergastrinaemia in rheumatoid patients appears to be based on an absence or severe reduction of gastric acid secretion. There is no ready explanation for the discrepancy between the findings of Rooney *et al.* (1976b) and our own results, although in contrast to our study Rooney and coworkers did not include rheumatoid patients with normal serum gastrin levels in their study. Nor did they show whether there is any relationship between serum gastrin levels and gastric acid secretion in their hypergastrinaemic patients. Generally, serum gastrin levels are increased in patients with reduced gastric production (Walsh and Grossman, 1975). Moreover, in patients with hypochlorhydria there is an inverse correlation between stimulated acid secretion rate and fasting

serum gastric concentration (Trudeau and McGuigan, 1971; Gedda-Dahl, 1974). The increased serum gastrin levels in these conditions are caused by the lack of inhibition of antral gastrin release due to the absence of gastric acid (Yalow and Berson, 1970; Fahrenkrug *et al.*, 1976).

In addition to the hypergastrinaemia a very high incidence of decreased gastric acid secretion was seen in our patients; only 50% of the patients had a normal maximum acid output (that is, higher than 10 mmol/h). The mean fasting serum gastrin level was found to be increased only if the MAO was lower than 2 mmol/h. In a study of nonrheumatoid patients the mean gastrin level was found to be raised if the MAO was less than 10 mmol/h, but only if MAO was lower than 2 mmol/h did the mean fasting gastrin reach very high levels (Gedda-Dahl, 1974). As in other studies (Trudeau and McGuigan, 1971; Gedda-Dahl, 1974) some of our patients with a MAO < 2 mmol/h had a normal fasting serum level of gastrin. Stockbrügger *et al.* (1977) found that in normogastrinaemic patients with achlorhydria the number of antral G-cells had not increased, probably as a result of coexisting antral gastritis.

In general it has been assumed that achlorhydria and severe hypochlorhydria are an expression of chronic atrophic gastritis (Bock *et al.*, 1963; Stockbrügger *et al.*, 1977). Louyot *et al.*, (1974) have established histological evidence of gastritis in 40% and hypochlorhydria or achlorhydria in 60% of a group of 50 rheumatoid patients. We abstained from taking gastric biopsies in our patients because it was considered unjustifiable to perform this procedure for experimental reasons only. Moreover, a small sample biopsy cannot conclusively exclude the presence of chronic atrophic gastritis. Atrophic gastritis, as demonstrated by others, resulting in a low gastric acid secretion can be accounted for either by the rheumatoid arthritis itself or by the long-term administration of anti-inflammatory drugs.

In the present study no relation was found between gastric acid secretion and the antirheumatic drugs given. Although in both studies no relation was found between the hyposecretion of gastric acid and the duration or activity of the rheumatic process, a possible role of the rheumatoid arthritis itself in the development of the hypochlorhydria cannot be excluded. Moreover, the increase of serum gastrin levels in untreated adjuvant arthritis in the rat also indicates a causative role of the inflammatory process itself (Rooney *et al.*, 1973c).

In conclusion, the high incidence of hypergastrinaemia in patients with RA is, in our opinion, due to achlorhydria or severe hypochlorhydria, and probably is the result of chronic atrophic gastritis.

References

- Bock, O. A., Richards, W. C., and Witts, L. J. (1963). The relationship between acid secretion after augmented histamine stimulation and the histology of the gastric mucosa. *Gut*, **4**, 112-114.
- Fahrenkrug, J., Schaffalitzky, O. B., Hornum, I., and Rehfeld, J. F., (1976). The mechanism of hypergastrinaemia in achlorhydria. *Gastroenterology*, **71**, 33-37.
- Gedda-Dahl, D. (1974). Fasting serum gastrin levels in humans with low pentagastrin-stimulated gastric acid secretion. *Scandinavian Journal of Gastroenterology*, **9**, 597-599.
- Hassan, M. A., and Hobsley, M. (1970). Positioning of subject and nasogastric tube during a gastric secretion study. *British Medical Journal*, **1**, 458-460.
- Hector, R. M. (1968). Improved technique of gastric aspiration. *Lancet*, **1**, 15-16.
- Lamers, C. B. H., and van Tongeren J. H. M. (1977). Comparative study of the value of the calcium, secretin and meal stimulated increase in serum gastrin to the diagnosis of the Zollinger-Ellison syndrome. *Gut*, **18**, 128-134.
- Louyot, P., Tamisier, J. N., Jeanpierre, J., Pourel, J., Zannetti, A., and Bertrand, P. (1974). Le compartement gastrique au cours des rhumatismes inflammatoires sous incidence médicamenteuse. *Revue du Rhumatisme*, **41**, 725-732.
- Nienhuis, R., and Mandema, E. (1963). A new serum factor in patients with rheumatoid arthritis: the antiperinuclear factor. *Annals of the Rheumatic Diseases*, **21**, 302-305.
- Rahfeld, J. F., Stadil, F., and Malmström, J. (1975). Gastrin heterogeneity in serum and tissue. In *Gastro-intestinal Hormones*, p. 34. Edited by J. C. Thompson. University of Texas Press: Austin and London.
- Rooney, P. J., and Dick, W. C. (1973a). Hypergastrinaemia in rheumatoid arthritis. *British Medical Journal*, **4**, 298.
- Rooney, P. J., Vince, J., Kennedy, A. C., Webb, J., Lee, P., Dick, W. C., Buchanan, K. D., Hayes, J. R., Ardill, J., and Connor, F. (1973b). Hypergastrinaemia in rheumatoid arthritis: disease or iatrogenesis? *British Medical Journal*, **2**, 752-753.
- Rooney, P. J., Dick, W. C., Imrie, R. C., and Buchanan, K. D. (1973c). An animal model for the study of the relationship between immunoreactive gastrin and inflammatory arthritis. *Nature*, **246**, 497-498.
- Rooney, P. J., Grennan, D. M., Sturrock, R. D., Brooks, P. M., and Dick, W. C. (1976a). Serum immunoreactive gastrin: specificity for rheumatoid arthritis, bimodality of distribution and failure of effect of anti-inflammatory drugs. *Annals of the Rheumatic Diseases*, **35**, 40-45.
- Rooney, P. J., Kennedy, A. C., Gray, G. H., Sturrock, R. D., Buchanan, K. D., and Dick, W. C. (1976b). Immunoreactive gastrin in rheumatoid arthritis; further observations on its identity, clinical specificity and relationship to gastric function. *Annals of the Rheumatic Diseases*, **35**, 246-250.
- Ropes, M., Bennett, J., Cobb, S., Jacox, R., and Jassar, R. A. (1959). 1958 Revision of diagnostic criteria for rheumatoid arthritis. *Arthritis and Rheumatism*, **2**, 16-20.
- Stadil, F., and Rehfeld, J. F. (1973). Determination of gastrin in serum: an evaluation of the reliability of a radioimmunoassay. *Scandinavian Journal of Gastroenterology*, **8**, 101-112.
- Stockbrügger, R., Larsson, L. I., and Lundquist, G. (1977). Antral gastrin cells and serum gastrin in achlorhydria. *Scandinavian Journal of Gastroenterology*, **12**, 209-213.
- Taylor, K. B., Roitt, I. M., Donlach, D., Couchman, A., and Shapland, C. (1962). Autoimmune phenomena in pernicious anaemia; gastric antibodies. *British Medical Journal*, **2**, 1347-1352.
- Trudeau, W. L., and McGuigan, J. E. (1971). Relations between serum gastrin levels and rates of gastric hydrochloric acid secretion. *New England Journal of Medicine*, **284**, 408-412.
- Walsh, J. H., and Grossman, M. I. (1975). Gastrin. *New England Journal of Medicine*, **292**, 1324-1334 and 1377-1383.
- Yalow, R. S., and Berson, S. A. (1970). Radio-immunoassay of gastrin. *Gastroenterology*, **58**, 1-14.