

## Gynaecomastia associated with cimetidine

R. W. SPENCE AND L. R. CELESTIN

*From the Department of Gastroenterology, Frenchay Hospital, Bristol*

**SUMMARY** Gynaecomastia has occurred unilaterally or bilaterally in five out of 25 male duodenal ulcer patients after more than four months treatment with cimetidine 1.6 g daily. All elected to continue treatment to 12 months and their breast enlargement regressed rapidly and disappeared after stopping treatment. During treatment all patients were found to have normal concentrations of plasma testosterone and oestradiol, and serum prolactin was normal in the two patients measured. Excision biopsy of the subareolar tissue in one patient revealed histology typical of the florid stage of gynaecomastia. Blockade of androgen-responsive receptors in the target organ appears to be the most likely mechanism involved.

Since Hall (1976) reported the development of gynaecomastia in two patients treated with cimetidine, various other cases of gynaecomastia and galactorrhoea have been reported (Bateson *et al.*, 1977; Delle Fave 1977; Sharpe and Hawkins, 1977). The total number of cases reported remains small and this report does not add materially to the total, as four of our cases were included in the overall report by Sharpe and Hawkins (1977) and Hall (1976) mentions two. Yet in a single long-term study we have encountered a 20% incidence of gynaecomastia in male duodenal ulcer patients.

### Patients

Twenty five male outpatients with endoscopically proven duodenal ulcer or severe duodenitis have been treated for 12 months with cimetidine 1.6 g daily administered as four divided doses. Five of these patients complained of soreness of one or both nipples associated with breast swelling after treatment intervals ranging from four to nine months. One patient has ankylosing spondylitis, while the other four have no concomitant disease. All elected to remain on treatment, preferring the minor symptom of breast soreness to their pretreatment symptoms, and gynaecomastia subsequently regressed rapidly in every case, the soreness disappearing within a few days of discontinuation of treatment. Only one of the patients experienced a temporary reduction in libido (the patient with ankylosing spondylitis). Unilateral excision biopsy was performed at the request of one of the patients two

weeks after he developed soreness of the nipple; light microscopic examination revealed moderate duct proliferation with some heaping up of the ductal epithelium in places, a little dilatation of some ducts and associated moderate hyperplasia of the peructidal connective tissue (Fig. 1), appearance typical of the early or florid type of gynaecomastia (Bannayan and Hajdu, 1972). Electron microscopy of the tissue revealed epithelial cells of the type usually found in breast and containing occasional typical milk granules (Fig. 2).

### Results of hormone assays

Estimation of plasma testosterone and oestradiol were performed in all five patients (Table). Because of the fluctuations that are known to occur in testosterone levels (Weitzman *et al.*, 1975) two daytime samples were obtained 30 minutes apart in cases 4 and 5 (shown in parentheses in the Table). Apart from case 5, where an isolated plasma testosterone value was above the upper limit of normal, all values obtained for plasma testosterone and oestradiol were within the stated normal limits and the ratio of free to protein-bound oestradiol was not increased in any case. In addition, in three patients plasma oestrone LH and FSH were within the range expected in normal males (V. H. T. James, personal communication). Plasma prolactin levels of daytime blood samples from cases 4 and 5 were measured (sample times corresponding with testosterone samples) and values were well within the normal range (Table).

During the course of treatment cimetidine blood concentrations were measured in all five patients in

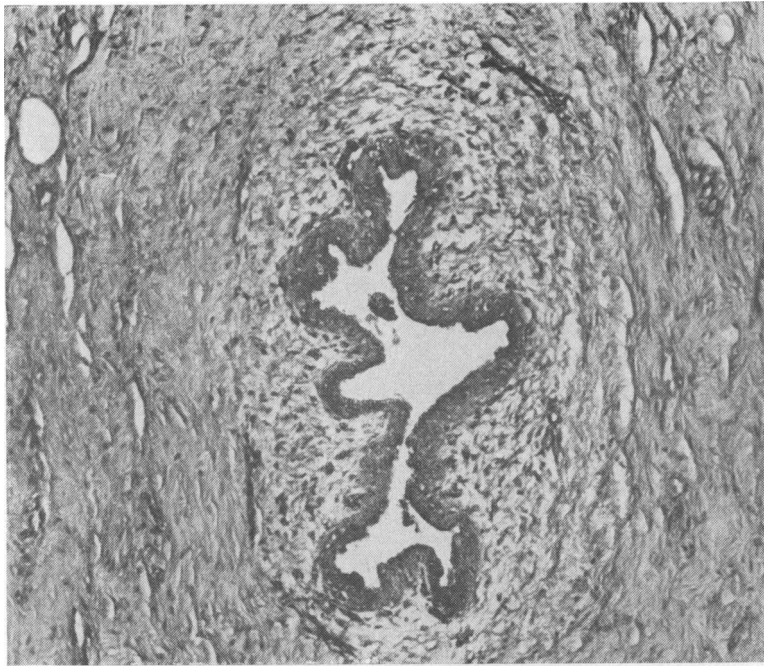


Fig. 1 Case 5. Light microscope photograph of a section of the biopsy showing a duct lined by heaped-up columnar epithelium and proliferation of surrounding connective tissue.  $\times 800$  (original magnification).

whole blood samples taken over six hours immediately after the ingestion of the first 400 mg dose of the day and concentrations tended to be lower than those found in another six similar patients in the study who did not develop breast soreness. Results in the gynaecomastia group were as follows: residual concentrations (from the previous day's dosing) 0 – 2.4, mean 0.6  $\mu\text{mol/l}$ ; peak concentrations 10 – 14, mean 12  $\mu\text{mol/l}$ . In the unaffected group the results were: residual concentrations 0 – 2.8, mean 2.1  $\mu\text{mol/l}$ , peak concentrations 14 – 20, mean 15.6  $\mu\text{mol/l}$  – (4  $\mu\text{mol/l}$  = 1  $\mu\text{g/ml}$ ).

### Discussion

The mechanism of drug-induced gynaecomastia remains unknown, though it has been reported in association with drugs as unrelated as spironolactone (Mann, 1963), digitalis (Le Winn, 1953), monoamine oxidase inhibitors (Arroyo, 1966), and vincristine (Smith and Barrett, 1967). There are various mechanisms by which breast enlargement may have arisen in this group of patients. First, refeeding, although a known cause of gynaecomastia, is an unlikely explanation in the present group, as only two patients showed an increase in body weight during treatment and one of these was already overweight before treatment. Secondly, cimetidine might interfere in some way with the release of androgens or disturb the androgen/oestrogen balance either by

increasing the rate at which androgen is metabolised to oestrogen, or by increasing the ratio of free to protein-bound oestrogen. Our data do not confirm such changes. In an earlier study no change was found in the plasma concentrations of testosterone in a different group (12) of our patients before and after six weeks' treatment with cimetidine at the same dosage as the present study (Sharpe and Hawkins, 1977). Similarly, 24 hour urinary excretion of testosterone in those patients remained within normal limits (unpublished data).

Thirdly, cimetidine might alter prolactin release but our results do not confirm this. In cases 4 and 5, samples for prolactin assay were taken at times during the day when circulating levels of the hormone would be expected to be declining after the physiological peak in the early hours of the morning (Sassin *et al.*, 1972). The values obtained were low and of the order of magnitude that would be expected in normal males during these hours. Delle Fave *et al.* (1977 a, b) and Bateson *et al.* (1977) have found serum prolactin concentrations increased above normal in both males and females after treatment with cimetidine, but reports are conflicting and neither Petrillo *et al.* (1977) nor Majumdar *et al.* (1978) have shown increased circulating prolactin after various intervals of cimetidine treatment. In a controlled study, Burland *et al.* (1978) have shown short-lived increases in serum prolactin in association with very high peak blood concentrations of

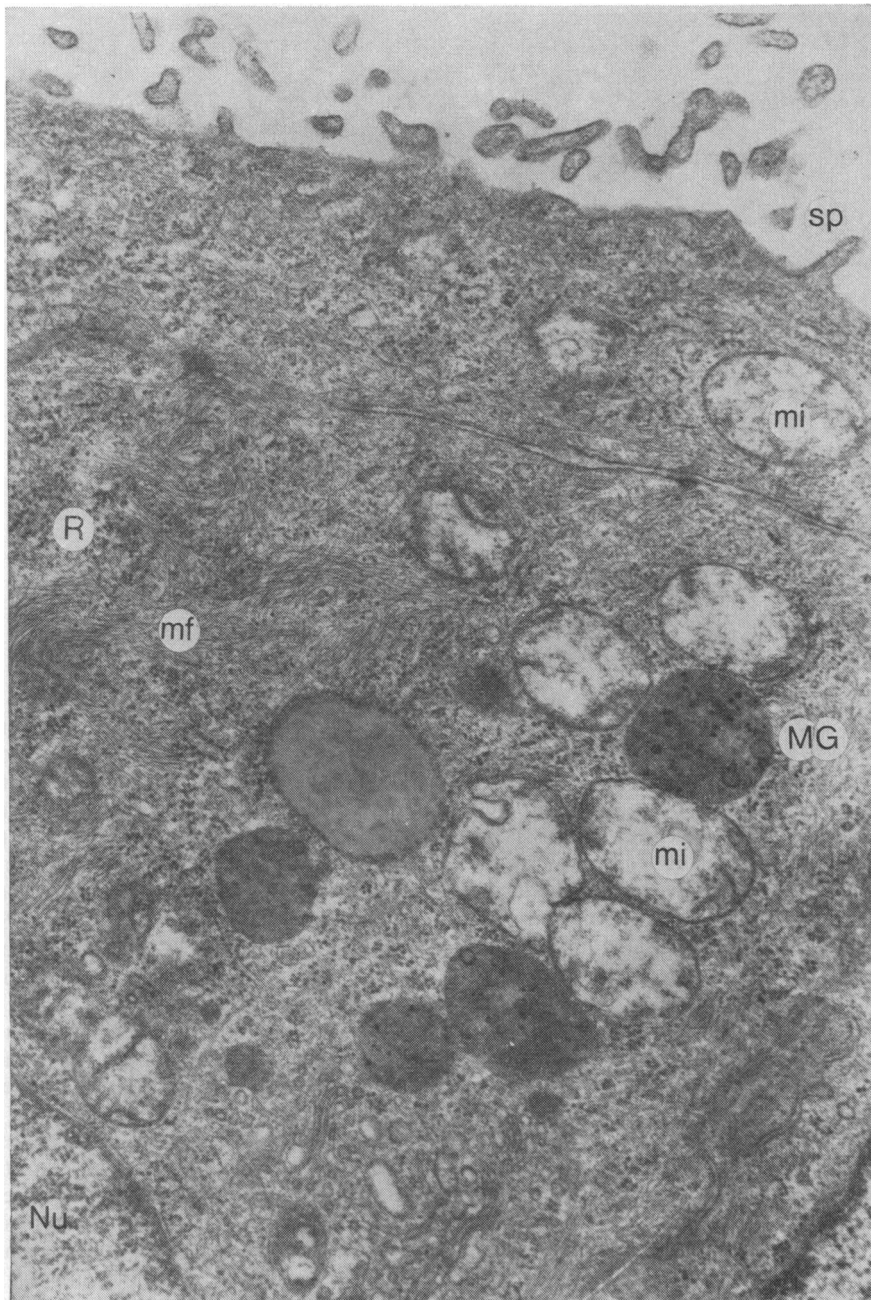


Fig. 2 *Electron micrograph of portions of two epithelial cells showing surface processes (sp), abundant cytoplasmic microfibrils (mf) and ribosomes (R), mitochondria (mi), milk granules (MG), and nucleus (Nu). Approximately  $\times 25\ 000$ .*

cimetidine after 400 mg intravenous bolus injections, but no increases after 800 mg oral doses.

The remaining possible mechanism involves the known weak anti-androgenic activity of the drug.

Cimetidine has no oestrogenic activity (Leslie and Walker, 1977) but has been shown to have weak anti-androgenic activity in rats and dogs as revealed by a reduction in the size and weight of the prostate

Table *Hormonal measurements in five duodenal ulcer patients with gynaecomastia*

Case no.	Testosterone (nmol/l)	Oestradiol (ng/100 ml)	Oestrone (ng/ml)	Prolactin (mU/100 ml)
1	14.6	9	—	—
2	19.4	8.8	—	—
3	10.7	4.9	5.1	—
4	19.4	—	—	—
	[24.8]	5.9	6.9	[14]
	[22.1]	6.6	5.1	[10]
5	28.5	—	—	28
	[37.0]	4.9	5.5	[16]
	[31.0]	—	—	[10]
Quoted laboratory normal range	10-32	< 1-12	—	< 35 9 am-9 pm

gland. It was suggested that this may be the result of blockade of androgenic receptors in the target organ. The dosages per kilogram body weight necessary to produce measurable reduction of prostate size in the dog were at least 20 times greater than the doses employed in our patients, so it is surprising that clinical sequelae should have resulted from the present dosage regimen. Certainly, testosterone levels in the blood in our patients were not reduced after prolonged treatment, so that the occurrence of gynaecomastia may be the result of blockade of receptors mediating the normal androgenic suppression of the responsiveness of breast tissue to normal (male) circulating levels of oestrogen, gonadotrophins, and prolactin. We consider this to be the most likely causative mechanism in the light of the available evidence.

Although anti-androgenic activity was demonstrable only in association with very high dose regimens in animals, blood concentrations of cimetidine in this study in the five affected patients tended to be lower than in the six similar patients who did not develop breast symptoms, so that the individual patient's liability to develop gynaecomastia appears to be influenced by more factors than blood concentrations of the drug alone. But, so far, gynaecomastia has not been reported in studies using lower dose regimens for four to six weeks only and it seems that it is likely to be encountered only in the long-term administration of higher doses of cimetidine. Gynaecomastia is on the whole a minor symptom, does not necessitate stopping treatment, and is readily reversible on discontinuing therapy.

We are grateful to Professor V. H. T. James of St. Mary's Hospital, Paddington, for androgen and oestrogen assays and to Professor K. Griffiths and Dr Graham Groom of the Tenovus Institute, Cardiff, for prolactin assays. Cimetidine blood concentrations were kindly measured by the Bio-

chemistry Department, Smith Kline and French Laboratories (Welwyn Garden City) whose Clinical Research Department also kindly supplied the cimetidine. Histological examination of the biopsy specimen was carried out by Dr R. J. Sandry and tissue for electron microscopy was prepared and photographed by D. A. McCormick.

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