anæmia was caused by the barbiturates she was taking. Both amylobarbitone sodium and quinalbarbitone sodium, the constituents of tuinal, are closely related chemically to primidone, sodium phenytoin, and phenobarbitone, but a megaloblastic anæmia has not previously been described in association with their use. The doses that this patient was taking (gr. 18–20 for 6–8 months) were, however, in excess of the usual doses given.

In view of the accumulating evidence that barbiturates interfere with the metabolism of folic acid, it appears desirable that the signs of early folic-acid deficiency should be sought in all patients who receive large doses of barbiturates for any length of time.

Summary

A woman, aged 30, who had acquired the habit of taking large doses of amylobarbitone sodium and quinalbarbitone sodium became critically ill with severe megaloblastic anæmia. Her serum-vitamin-B_{12} level before treatment was normal, and she did not respond to treatment with vitamin B_{12}. Her anæmia, however, responded rapidly to treatment with folic acid.

Her diet was adequate and no significant impairment of intestinal absorption was found.

We wish to thank Dr. I. Chanarin, of the department of pathology* (hæmatology) for the folic-acid assay; Dr. E. Lester Smith, of the research division of Glaxo Laboratories Ltd., for the labelled vitamin B_{12}; and Miss Barbara Anderson, B.SC., for help with the radioactive measurements.

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AGRANULOCYTOSIS DURING TREATMENT WITH PACATAL

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'PACATAL,' 9-(1-methyl-3-piperidylmethyl) phenothiazine, a synthetic compound, is a new tranquillising drug recently introduced in this country. Because of the increasing and widespread use of such drugs it seems desirable to draw attention to any serious complication which may arise during their use. We are therefore reporting the following case of agranulocytosis developing during treatment with pacatal:

A married woman, aged 35, was admitted to this hospital on June 4, 1956, with about a year's history of severe depression. She was in good physical health. On this occasion, as on two previous admissions, she did not respond to electroconvulsive therapy.

Treatment with pacatal 25 mg. three times daily was begun on July 10 and the dosage was increased to 50 mg. three times daily on July 24. On Aug. 23, after 5·55 g. of pacatal had been given, this treatment was stopped because a routine blood-count showed 3000 white cells per c.mm. (polymorphs 53%).

Progress.—A week later she had 2600 white cells per c.mm. Two days later, on Sept. 1, the patient complained of sore throat and headache and looked pale and ill. She had a temperature of 99°F, pulse-rate 100, and respirations 22 a minute. Her pharynx and fauces were inflamed. Examination of the blood showed Hb 83% and white cells 900 per c.mm. (polymorphs 1%). She was given intramuscular injections of sodium pentose nucleotide 10 ml. and penicillin 500,000 units every six hours. During the next three days she had irregular low-grade pyrexia and developed necrotic pharyngeal ulcers. On Sept. 4 streptomycin was given in addition to penicillin because a profuse growth of *Escherichia coli* resistant to penicillin but sensitive to streptomycin was cultured from her throat. At this time there was a definite improvement in her general condition, and from then on her white-cell count rapidly returned to normal. Nine days after the diagnosis had been made no abnormality was found. The changes in her blood picture were as follows:

Date	*White cells per c.mm.*	*Polymorphs (%)*
Sept. 1	900	1
Sept. 2	850	None
Sept. 3	1000	2
Sept. 4	1600	2
Sept. 5	1400	10
Sept. 7	3500	25
Sept. 10	11,000	50

Since this patient developed agranulocytosis during treatment with pacatal, it seemed reasonable to conclude that there was a causal relationship between the drug and the development of this serious complication. So far as we know, no account of agranulocytosis due to pacatal has yet been published in this country, perhaps because of the lag between the introduction of a new drug and the discovery of dangerous side-effects. It is clearly important to do routine blood-counts on patients treated with pacatal and to caution them to report any departure from their customary state of physical health, such as the development of fever, sore throat, or local sepsis.

We are grateful to Dr. I. R. Nussbaum for permission to publish, and to the laboratory staff of Rainhill Hospital for the investigations.

A STEROID-INDUCED GASTRIC ULCER*

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DURING investigations into the acute effects of corticotrophin and adrenocortical steroids on gastric secretion (Hirschowitz et al. 1955a), one of the subjects of our experiments developed a prepyloric gastric ulcer. The findings are presented here because there is little published information about changes in gastric secretion and in pepsinogen levels in the plasma and the urine before and immediately after exacerbations of peptic ulcer.

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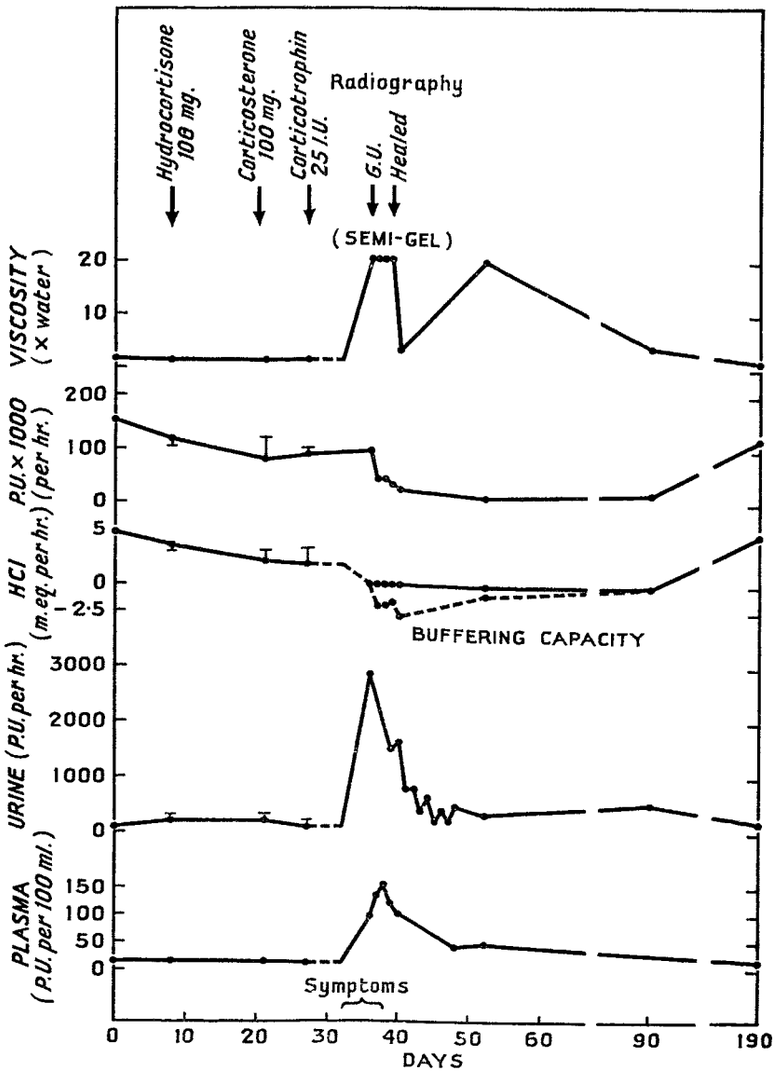


Fig. 1—Changes in gastric secretion and urine-pepsinogen and plasma-pepsinogen levels before, during, and after healing of steroid-induced prepyloric gastric ulcer.

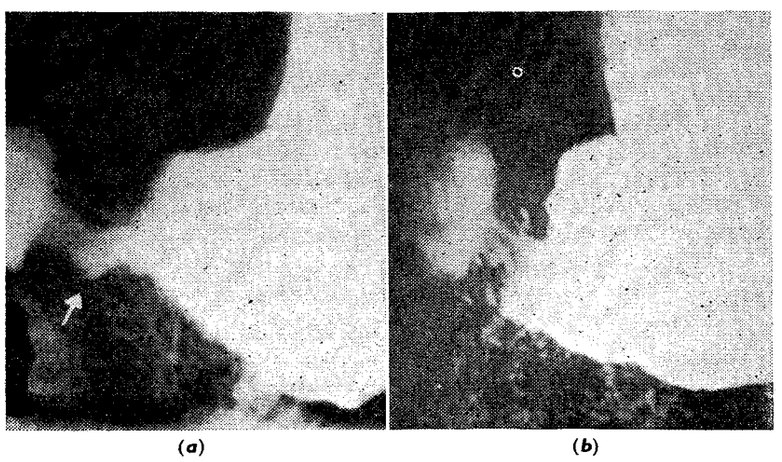
The course of the ulcer and the laboratory findings in this patient were strikingly similar to those seen in another subject, who developed a postbulbar duodenal ulcer while receiving corticotrophin (Hirschowitz et al. 1955b), and lend support to the conclusions drawn from the earlier observations on the genesis and healing of steroid-induced ulcers.

Methods

The patient had four 13-hour studies (on days 1, 8, 20, and 27) in which basal gastric secretion was measured. In the first study the vehicle alone (1·0% alcohol and 2·5% dextrose in 0·45% saline solution) was infused for 13 hours. In the subsequent three studies infusion of the vehicle alone for 5 hours was followed by infusions, during 8 hours, of hydrocortisone 100 mg., corticosterone 100 mg., and corticotrophin 25 I.U., each in 1000 ml. of vehicle.

The volume, acid content, pepsin content, and viscosity of the gastric juice, as well as the plasma and urinary pepsinogen, were measured by the methods previously described (Hirschowitz et al. 1955b, Hirschowitz 1955). Buffering capacity of samples of gastric juice of pH over 3·5 was measured by electrometric titration against 0·1 N hydrochloric acid to pH 3·5.

Sodium and potassium concentrations were measured on the Baird internal standard flame photometer; eosinophils were counted by using phloxine in propylene glycol; and plasma-cholinesterase levels were estimated by the method of Michel (1949).



(*a*) (*b*)

Fig. 2—Stomach radiographs: (*a*) on day 31, showing prepyloric crater (arrow) on 4th day of symptoms; and (*b*) on day 35, showing complete healing of ulcer.

Case-report

The subject was a male medical student, aged 23, who had had no previous gastric symptoms of any kind. The mean changes from the control values induced by hydrocortisone, corticosterone, and corticotrophin in the hourly output of hydrochloric acid and of pepsin are indicated in fig. 1 by the vertical lines at each point: hydrocortisone caused a small decrease in both hydrochloric acid and pepsin, whereas corticosterone and corticotrophin caused a moderate increase in both. In none of these experiments was there any unusual response in the eosinophil-count, hæmatocrit, urinary electrolytes (Na and K), or excretion of pepsinogen, or any change in plasma-pepsinogen or plasma-cholinesterase levels, either before or immediately after development of the ulcer. During the experimental period and until 4 days after the last experiment (corticotrophin) the subject of the experiment had no symptoms.

Onset and Course.—On the morning of the 5th day after corticotrophin he complained of epigastric pain, hypersalivation, and nausea. Solid food aggravated the pain for the first day or two, and milk afforded partial relief, but the pain persisted despite the patient's taking 'Probanthine' 15 mg. thrice daily for the first 2 days. He took no other medication, and therapy after the first 2 days was confined to a bland diet for the next week. A radiograph of the upper-gastrointestinal tract on the 4th day after the onset of symptoms showed a moderately large prepyloric crater (fig. 2*a*). 3 days later the patient had no symptoms, and radiography next day showed that the ulcer was completely healed (fig. 2*b*). No further symptoms developed in the next 15 months.

Laboratory Findings.—No laboratory studies were made in the 4 days preceding the onset of symptoms or in the 2 following days. Serial daily 1-hour basal gastric analyses were obtained in the next 5 days and three more in the next 5 months (see fig. 1). The changes in gastric secretion and in plasma and urinary pepsinogen immediately after the onset of the ulcer were striking and almost identical with those in a similar case reported previously (Hirschowitz et al. 1955b). The secretion of hydrochloric acid ceased, pepsin secretion diminished, and the viscosity of the gastric juice increased to the point where some specimens had to be cut with scissors to allow separation of samples for pH measurements. At the same time the plasma-pepsinogen and urine-pepsinogen levels, which had been normal 4 days before the ulcer appeared, rose extremely high. 2 months after the ulcer had healed the basal gastric juice still contained no acid and little pepsin, and the plasma-pepsinogen and urine-pepsinogen levels were still moderately raised. Five months after the ulcer, gastric secretion and the plasma-pepsinogen and urine-pepsinogen levels had reverted to normal.

Discussion

As in the similar case of a corticotrophin-induced ulcer reported previously (Hirschowitz et al. 1955b), no abnormalities in the volume or composition of gastric secretion or in the plasma-pepsinogen and urine-pepsinogen levels were noted in the 4 weeks preceding the onset of the ulcer; though the possibility cannot be ruled

out that changes may have taken place in the 4 days immediately before symptoms started.

The changes after the ulcer were very similar to those seen in the previously reported case and consisted in an initial hypersalivation, probably manifesting vagal overactivity, followed shortly by achlorhydria and a decrease in pepsin, and a great increase in gastric mucus. The decrease in gastric pepsin contrasted with the increases in plasma-pepsinogen and urine-pepsinogen levels, suggesting a reversal of the secretion gradient of the peptic (chief) cells of the gastric mucosa.

The ulcer healed rapidly, and there was radiological evidence of healing (fig. 2b) of the ulcer 4 days after a crater was seen and 7 days after the first symptoms.

There is no evident difference between the manifestations of these corticotrophin-induced ulcers and those of many spontaneous ulcers. It is therefore possible that a "spontaneous" peptic ulcer may be initiated by endogenous release of corticotrophin in response to physical or mental stress (Gray et al. 1951). Our observations, however, provide no support for the view that the rôle of corticotrophin in the genesis of peptic ulcer is mediated by any abnormal changes in the secretion of acid or of pepsin by the stomach.

The reason why some acute ulcers heal rapidly while others relapse and become chronic is unknown. Some inkling of a possible mechanism for the emergence of chronicity in ulcers is provided by the observed changes in the composition of gastric juice in the two patients whose ulcers healed so promptly. The healing was in each instance associated with virtually complete substitution of thick mucus for the normal constituents of the gastric juice. In contrast, most patients with chronic duodenal ulcers continue to secrete gastric juice with relatively high concentrations of acid and normal concentrations of pepsin. Though there is no evidence that an increased secretion of acid and pepsin precedes and causes the initial or recurrent breakdown of the gastric or duodenal mucosa, it is quite conceivable that the continued secretion of acid and pepsin may prevent the healing of an ulcer which would have healed rapidly if mucus had taken the place of acid and pepsin in the gastric juice. The cause of failure to heal and the emergence of chronicity might therefore reside in a deficient substitution of mucus for acid and pepsin in the gastric secretions.

Summary

A case of a steroid-induced prepyloric gastric ulcer in a previously healthy male medical student, aged 23, is described, with observations on gastric secretion and plasma-pepsinogen and urine-pepsinogen levels before and after the appearance, and during and after the healing, of the ulcer.

These observations are compared with a previously reported and very similar case.

It is concluded that changes in gastric secretion of acid and pepsin played little part in the genesis of the ulcers.

Healing of the ulcer, which took 7 days, was accompanied by the substitution of mucus for normal gastric juice. This is regarded as probably a defence reaction, whose failure may eventually lead to chronicity in peptic ulceration.

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Preliminary Communications

EFFECT OF CARBUTAMIDE ON SERUM-CHOLESTEROL LEVEL IN DIABETES MELLITUS

In the course of a clinical trial of carbutamide (B.Z.55) in diabetes mellitus, we have noticed changes in the serum-cholesterol level. In some, though not all, patients the serum-cholesterol falls during the first few days of therapy, and then rises rapidly, tending to regain its original level even if the drug is still given. So far, these events have been studied in only six patients, four of whom showed the effect; and we are well aware that serum-cholesterol levels sometimes fluctuate inexplicably. Nevertheless, we think it desirable to bring our findings to the notice of others using carbutamide and similar compounds at a time when these drugs are still being intensively investigated.

All the patients were studied in hospital while taking a diet in which the content of fat and carbohydrate was fixed. The fat was not analysed for its derivation or composition, but it did not differ materially either in type or in quantity from that taken by the public as a whole. The distribution of fat and of carbohydrate among the meals was constant from day to day.

The control of the diabetic state was judged mainly by the 24-hour output of sugar in the urine; but blood-glucose was estimated $2^1/_2$ hours after breakfast, daily or at not longer than 3-day intervals. At the same time, blood was withdrawn for serum-cholesterol determination.

After a control period of not less than 4 days on the fixed diet, carbutamide was given orally in a single dose daily $2^1/_2$ hours after breakfast, starting with 5 g. on the first day, 3 g. on the second day, and 1 g. on subsequent days. If the drug did not adequately control the diabetes, a few days without treatment were allowed to elapse before starting insulin. While insulin was being given, the same régime was followed.

Here we shall describe only two cases, the first showing a good response of the diabetes to carbutamide, the second a very small response.

Case 1.—A woman, aged 69. No family history of diabetes. Height 5 ft. $2^1/_2$ in. Weight 8 st. 2 lb. Her maximum weight, 10 st. 7 lb., was at the onset of the diabetes 7 years previously. Control by diet alone had been effective until shortly before the carbutamide trial. On admission, the fasting blood-glucose was 274 mg. per 100 ml. The urine contained no ketone. No diabetic or vascular complications were found. Fig. 1 shows how the drug affected the daily urinary sugar output and the serum-cholesterol level. (The blood-glucose estimations are not shown in the charts but the changes corresponded approximately with the urinary sugar output.)

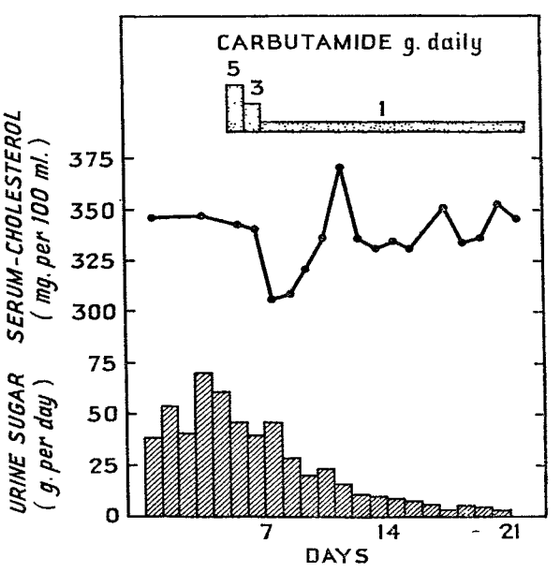

Fig. 1.

Case 2.—Man, aged 58. No family history of diabetes. Height 5 ft. $6^1/_4$ in. Weight 9 st. 8 lb. His maximum weight