Anaemia 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 anaemia 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 anaemia. Her serum-vitamin B12 level was found.

**REFERENCES**


**AGRANULOCYTOSIS DURING TREATMENT WITH PACATAL**

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'Pacatal,' 9-(1-methyl-3-piperidylmethyl) phenothiazine, a synthetic compound, is a new tranquillisng 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 a history of severe depression. She was in good physical health. On this occasion, 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.m.m. (polymorphs 53%).

**Progress.—**A week later she had 2600 white cells per c.m.m. 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.m.m. (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 her pharynx and fauces became inflamed. Examination of the blood showed Hb 83% and white cells 900 per c.m.m. (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:

<table>
<thead>
<tr>
<th>Date</th>
<th>White cells per c.m.m.</th>
<th>Polymorphs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept. 1</td>
<td>900</td>
<td>4</td>
</tr>
<tr>
<td>Sept. 2</td>
<td>850</td>
<td>None</td>
</tr>
<tr>
<td>Sept. 3</td>
<td>1000</td>
<td>2</td>
</tr>
<tr>
<td>Sept. 4</td>
<td>1000</td>
<td>2</td>
</tr>
<tr>
<td>Sept. 5</td>
<td>1400</td>
<td>10</td>
</tr>
<tr>
<td>Sept. 7</td>
<td>3500</td>
<td>25</td>
</tr>
<tr>
<td>Sept. 10</td>
<td>11,000</td>
<td>50</td>
</tr>
</tbody>
</table>

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 peptic 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.

* This study was aided by a grant from the United States Public Health Service No 4288 (C).
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 urine 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).

**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 outputs 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, hematocrit, urinary elec-

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. 2a). 3 days later the patient had no symptoms, and radiography next day showed that the ulcer was completely healed (fig. 2b). 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 follow-

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
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 cases, though not at all, patients with the serum-cholesterol level 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 effec-
tive until shortly before the carbuta-
mide trial. On admission, the fasting blood-glucose was 274 mg. per 100 ml. The urine contained a small amount of ketone. No diabetic or vesicular 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.)

Case 2.—Man, aged 58. No family history of diabetes. Height 5 ft. 6 1/4 in. Weight 8 st. 7 lb. His maximum weight