November 14) and treated symptomatically with intravenous glucose-saline, pethidine, and morphine.

In February, 1950, he was again in hospital, after another crisis which had lasted one week. Examination of the cerebrospinal fluid on February 17 showed: cells, 1 per c.mm.; protein, 30 mg. per 100 ml.; globulin, no increase; Wassermann reaction, 0.2 ml. negative; 0.5 ml. negative; 1 ml. negative; gold sol, 0000000000. At this time a test meal demonstrated histamine-fast achlorhydria, and a positive benzidine reaction was obtained with each specimen withdrawn. Radiography after a barium meal revealed a filling defect on the lesser curvature of the stomach, the appearance being more suggestive of carcinoma than of a simple lesion; gastroscopy confirmed the presence of an outgrowth on the lesser curvature (Dr. D. M. F. Batty).

Accordingly a second laparotomy was performed on March 24 (Mr. J. S. Jeffrey), and a diffuse area of thickening was found in the stomach wall on the lesser curvature with no enlargement of the associated glands. The distal two-thirds of the stomach was resected and subsequent histological examination showed the presence of a well-differentiated adenocarcinoma, with no evidence of spread. During convalescence the patient experienced further smouldering episodes of epigastric pain and vomiting.

He returned to his previous occupation and remained well until the first week of August, when continuous acute upper abdominal pain returned. On August 11 he re-entered hospital, and a further barium-meal examination showed a possible stenosis of the stoma. It was feared that there had been an extension of the neoplastic process, and a third laparotomy was performed (Professor Mercer), but no abnormality was found.

During the subsequent period of convalescence the crises continued to occur and were treated with morphine or pethidine hypodermically; neither drug gave complete relief from pain. Examination of the cerebrospinal fluid on December 27 showed: cells, 2 per c.mm.; protein, 50 mg. per 100 ml.; Wassermann reaction, negative; gold sol, 0000000000.

Finally, on January 8, 1951, the patient was admitted to the department of surgical neurology, where after a preliminary period of observation a right antero-lateral chordotomy was done at C. 3-4 level (Mr. F. J. Gillingham). This resulted in loss of pain and temperature sensation below the level of C. 8 on the left side, light touch remaining unimpaired. Five weeks later he left hospital and, after a short convalescence, resumed his former employment as a deep-sea fisherman. On March 27 the blood Wassermann reaction and Kahn test were negative. Nine months later he stated that he had had no further symptoms and had "never felt better."

Summary

A case of tabetic gastric crises is described which exhibited the following noteworthy features: (1) The occurrence of Argyll Robertson pupils as the only clinical sign of neurosyphilis in a patient with severe gastric crises. (2) A tendency for the crises to become more frequent and incapacitating, although both blood and spinal fluid became ultimately normal during adequate antisyphilitic treatment. (3) Suspicions of organic intra-abdominal disease strong enough to lead to laparotomy on three occasions and the discovery of a gastric carcinoma in a very early stage at the second operation. (4) Cessation of crises following unilateral chordotomy.

I wish to thank Dr. R. C. L. Batchelor for permission to publish this case.

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TOXIC EFFECTS OF PHENYLBUTAZONE

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Whilst the aetiology of rheumatoid arthritis remains an unsolved problem new therapeutic measures will constantly be tested for their power to alleviate its symptoms and in the hope of throwing some light on its causation. Phenylbutazone ("butazolidin") has lately been advocated as a drug which is likely to be a potent weapon in the treatment of rheumatic conditions (Currie, 1952).

Since the release of the drug for general use an increase in toxic reactions, occurring in from one-fifth to one-third of patients, has been reported (Loxton *et al.*, 1952; Kuzell *et al.*, 1952; Rhys Davies *et al.*, 1952; Cudkovicz and Jacobs, 1953). A warning of the dangers of its uncontrolled use was given by Hart and Johnson (1952). The principal untoward reactions are rashes, anorexia, nausea, abdominal pain, looseness of the stools, and reactivation of peptic ulcers with bleeding. As phenylbutazone is closely allied to amidopyrine chemically, it is not surprising that agranulocytosis, fatal in two instances, has been reported in several patients (*British Medical Journal*, 1952; Bershof and Oxman, 1953; Etess and Jacobson, 1953; Stifel and Burnheimer, 1953). Oedema due to sodium retention is a common but avoidable side-effect (Green and Williams, 1953).

Present Investigation

This paper is a record of our experiences with phenylbutazone during the past six months. The drug can be given either by mouth or by intramuscular injection, but as the majority of patients treated were out-patients the former route was usually employed. All patients were warned of possible side-effects and were asked to restrict their salt intake; those who gave a definite history of peptic ulceration or cardiovascular or renal disease were not treated with the drug. Three patients were suffering from diabetes, which was not affected by phenylbutazone.

The series consisted in 109 patients (79 women and 30 men), their ages ranging from 12 to 73 years (average age 49 years). Of these patients 86 suffered from rheumatoid arthritis, 19 from osteoarthritis, and 3 from gout. One patient had a ligamentous strain of the knee. In 18 patients phenylbutazone was combined with cortisone, but in only 4 was the effect good enough to allow the hormone to be completely withheld.

The drug was given to 102 patients by mouth in tablets containing 0.2 g. in daily doses ranging from 0.2 to 1.2 g. (average dose 0.6 g.). Seven received intramuscular injections of 1 g. on four alternate days, followed by weekly injections. All patients were seen first at weekly, then fortnightly, and, later, monthly intervals. A check was kept on the white blood count and the sedimentation rate.

Results

Symptomatically 59 patients were greatly improved by phenylbutazone, but in none was there any associated fall in the sedimentation rate. In 15 improvement was only slight, in 25 the drug had no beneficial effect, and in 10 toxic reactions occurred before any therapeutic effect could be noted.

Toxic side-reactions severe enough to necessitate stopping the drug occurred in 46 patients. The following reactions, usually in various combinations, were noted: (1) Twenty-one patients noticed severe anorexia and upper abdominal pain, one of these also having looseness of the bowels. (2) Seventeen complained of dryness of the mouth and throat, and were found to have redness of the anterior faucial pillars and uvula. Two of these had actual ulceration, which in one caused a submaxillary abscess requiring surgical drainage. Blood counts remained normal in this group. (3) Sixteen developed punctate erythematous rashes. (4) Two had enlargement of the glands in the posterior triangles of the neck. (5) One patient suffered from severe vertigo. (6) One developed granulopenia, recovering after the drug was withheld; white blood count 1,700, neutrophils 39%. The white count before treatment was 12,000, neutrophils 79%. Several patients showed a transient eosinophilia. (7) Three patients had exacerbations of the rheumatoid lesions of their hands.

Sodium retention was thought to be responsible for the slight gain in weight noticed in most patients, but only two developed pronounced oedema. This disappeared in one after salt restriction, which had not been carried out as requested, but persisted despite these measures in the other.

Response to Phenylbutazone Compared with Toxic Reactions

Response	No.	No. of Toxic Reactions Noted
<i>In All Patients Treated</i>		
Complete symptomatic relief	31	15
Marked	28	11
Analgesic effect, similar to aspirin ..	15	7
No symptomatic relief	25	3
Drug not given long enough to observe therapeutic effect	10	10
Total	109	46
<i>In Patients Suffering from Rheumatoid Arthritis</i>		
Complete symptomatic relief	28	14
Marked	20	8
Analgesic effect, similar to aspirin ..	11	6
No symptomatic relief	20	2
Drug not given long enough to observe therapeutic effect	7	7
Total	86	37

These reactions occurred on the average after three weeks, and in only two patients after three months. They were not related to dose or mode of administration, and promptly disappeared when the drug was omitted. A change from oral to parenteral therapy seemed to make no difference.

The most distressing aspect of phenylbutazone is apparent when its antirheumatic effects are compared with its toxic effects: the drug had to be withheld from nearly half the patients gaining most benefit from it, and those suffering from rheumatoid arthritis relapsed after its withdrawal (see Table).

Conclusion

We have found, as have most other authors, that phenylbutazone is a most effective weapon in combating the symptoms of rheumatoid arthritis and acute gout. However, it induced in nearly half of our patients toxic reactions severe enough to make further therapy dangerous. Nevertheless its trial in chronic disabling conditions seems justifiable, since there are a large number of patients who derive benefit without toxic manifestations; scarce supplies of A.C.T.H. and cortisone may thus be conserved. It has recently been suggested that if used in doses not exceeding 0.4 g. every 1 to 10 days only transient rashes are likely to be encountered (Lawrence, 1953). This mode of administration certainly deserves further trial.

Summary

Phenylbutazone was given to 109 patients suffering from various rheumatic conditions. Forty-six patients suffered from toxic reactions. These occurred in nearly

half of those deriving great benefit. The diabetic condition of three patients receiving the drug was not affected by it. Its use is justifiable where careful and continuous control is possible.

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TOXIC EFFECTS OF PHENYLBUTAZONE WITH SPECIAL REFERENCE TO DISORDERS OF THE BLOOD

BY

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During the past nine months many reports on the use of phenylbutazone ("butazolidin") in rheumatoid arthritis and allied diseases have appeared in the literature. The incidence and severity of toxic reactions have varied widely, as may be seen from the Table printed overleaf. Thus Peebles-Brown and Currie (1952) described only five toxic effects out of 280 patients (an incidence of 1.8%). On the other hand, Cudkovicz and Jacobs (1953) reported an incidence of 52%, and Stephens *et al.* (1952) one of 44%. Details of the 356 reactions in 1,526 patients have now been reported—an average incidence of 22%. This figure agrees closely with the estimate of Loxton *et al.* (1952).

The most frequent complications are by now well recognized. Oedema occurred in 84 patients; it is due to retention of sodium and water, and has often precipitated cardiac failure. Various gastro-intestinal symptoms (nausea, vomiting, diarrhoea, "gastritis") are also common, but rarely have serious consequences; more grave, however, is the reactivation of peptic ulcer (17 patients) and haematemesis and melaena (13 patients). The latter was the cause of death in one case reported in the *British Medical Journal* (1952). Jaundice has been recorded in six patients. Skin rashes are common (51 patients) and seem to be protean in variety. Miscellaneous effects include vertigo, euphoria, conjunctivitis, haematuria, albuminuria, "haemorrhagic myelitis," and stomatitis.

The effects on the blood seem to include depression of any or all of the cellular elements. Thus Stephens *et al.* (1952) reported a fall in haemoglobin of 1 g. per 100 ml. or more in 18 out of 188 patients, and a fall in the platelet count below 100,000 per c.mm. was even more common (31 patients). Eleven cases of frank agranulocytosis, with one death, have so far been recorded, and there have been several other cases of granulocytopenia.

The case histories of two patients are described below; the first developed aplastic anaemia, and the second agranulocytosis, during treatment with phenylbutazone. The former seems to be the first case of this complication described in the literature, if one excludes the case of Kuzell *et al.* (1952a); this patient was already suffering