proportion (60%), although the total numbers were diminishing. It was during this period that the one haematemesis occurred in a patient whose barium-meal examination revealed nothing abnormal. After one year the only toxic effects observed were gastro-intestinal although no proved peptic ulcers occurred. However, after the third year no further intolerance developed, although it must be remembered that only 38 of the original 315 patients were continuing to take the drug, and these must therefore represent a residue of highly tolerant patients. Rash, when it occurred, usually did so in the first three months of administration. None were seen after six months. Oedema, however, occurred at any time during the first year.

Summary

315 patients with rheumatoid arthritis treated with phenylbutazone in an average dose of 300 mg. a day have been studied over a period of at least four years; the reasons for withdrawal of the drug are analysed.

The overall intolerance rate was 27.7%, but this accounted for less than one-third (31.4%) of the cases in which the drug was withdrawn, the other important causes being inadequate relief (33.6%) and remission (11.2%).

Gastro-intestinal intolerance was the most frequently observed symptom of intolerance, and after more than one year of continuous administration it was the only form of intolerance seen.

38 patients (12.1%) continued to take phenylbutazone for over four years with satisfactory control of symptoms and without intolerance.

We are grateful to Dr. W. S. Tegner for allowing us to make use of the patients under his care.

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"Diagnosis in indigenous medical systems is aimed basically at discovering the occult agency responsible and seldom involves careful physical examination or history-taking as in scientific practice, but, particularly in Africa, is often based on divination by throwing cowrie shells, seeds, or bones, which may be carved out of wood or be genuine, as, for example, the talus bones of the lion and koodoo which are highly prized in parts of Rhodesia, or by using different forms of trance, crystal gazing, dream interpretation, or possession. Thus among the Fore people in the hinterland of New Guinea Gajdusek and Zigas record that divination to diagnose the sorcerer thought to be responsible for a case of kuru is based on the examination of end results of rats that have been roasted in bamboo cylinders." (D. B. Jelliffe and F. J. Bennett, "Indigenous Medical Systems and Child Health," *J. trop. Pediat.*, August, 1960.)

HYPERURICAEMIA DUE TO PYRAZINAMIDE

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Streptomycin, isoniazid, and sodium P.A.S. are the three drugs most commonly employed in the treatment of tuberculosis, and their value and efficacy is well known. A number of second-line drugs are also available; their use is reserved for those situations where, for one reason or another, resistance has developed to two or all three of the above drugs, and for those cases where the development of toxic side-effects or the patient's refusal to continue taking one or more of these drugs makes their suspension necessary.

The additional drugs include viomycin, cycloserine, pyrazinamide, and 1314 TH (alpha-ethyl-thioisonicotinamide). Unfortunately, several of these have their usefulness limited by undesirable side-effects, and in some there is only a small margin, often difficult to calculate, between the therapeutic and a toxic dose.

Our attention was focused upon one aspect of pyrazinamide treatment when a man aged 55 under our care, who because of multiple resistances had been treated with a combination of pyrazinamide and 1314 TH for five months, developed pains in his feet and a small tophus-like lesion in the left ear in August, 1959. Investigations revealed an elevated serum uric acid. It was subsequently shown that his symptoms and signs were in fact unrelated to this hyperuricaemia, and the earlier suspicion of a gouty diathesis was not confirmed. After the discovery of hyperuricaemia in this patient, a number of other patients, also under treatment with pyrazinamide, were investigated from this aspect.

Chemistry and History of Pyrazinamide

In 1945 nicotinamide was found to have tuberculo-static activity in guinea-pigs and mice, and in 1947 there followed the investigation of many allied drugs. In 1952 an analogue of nicotinamide—pyrazinamide—was found to be more active in mice, and the first clinical trial of it was reported (Yeager *et al.*, 1952).

Pyrazinamide (pyrazinoic acid amide) is a diazine carboxamide chemically related to nicotinic acid and has the following structural formula:

It is an odourless, white crystalline powder stable indefinitely at ordinary temperatures. It is soluble in water (15 mg./ml. at 25° C.) to form a neutral colourless solution stable at room temperature.

Pyrazinamide is hydrolysed in the body, the primary product being pyrazinoic acid, which reacts with ferrous

ammonium sulphate, producing an orange-red complex that absorbs light, in accordance with Beer's law, at a wavelength of 460 m μ . Determination of the blood and urine levels is based on this reaction (Allen *et al.*, 1953).

The *in vitro* activity of pyrazinamide is not high, and resistance to H 37 Rv develops rapidly (Solotorovsky *et al.*, 1952).

Clinical Use of Pyrazinamide

Many reports of the clinical use of pyrazinamide have appeared, from which the following conclusions may be drawn.

When administered alone there is a moderate antituberculous effect, probably lying between that of P.A.S. and streptomycin, but this is short-lived owing to the rapid development of resistance in a large proportion of cases (Potter and Chang, 1955). Schwartz and Moyer (1954) considered that the combination of pyrazinamide and isoniazid was equal to any other antituberculous drug regime, but that neither P.A.S. nor streptomycin

enhanced the effectiveness of pyrazinamide; nor did pyrazinamide delay the emergence of P.A.S. or streptomycin-resistant strains.

In a report of the American College of Physicians (1957) the recommended dosage of pyrazinamide is 30–40 mg./kg. of body weight, the total daily dosage not exceeding 3 g.

The most serious toxic effect of pyrazinamide is upon the liver. The U.S. Public Health Ser-

vise Tuberculosis Therapy Trial (1959), in a series of 780 patients, reported an incidence of hepatic toxicity in 2–6%, depending upon the dosage employed.

In a report by the Committee on Therapy of the American Trudeau Society (Amberson *et al.*, 1957) a chart summarizing toxicity in 13 published clinic reports on 1,070 patients shows 33 (3.1%) instances of jaundice, 22 (2%) of joint pain, 8 (0.7%) of haemoptysis, and 43 (4%) of increased bromsulphthalein excretion without clinical jaundice.

Transaminase estimations carried out at weekly intervals provide a most sensitive indicator of early damage and should be used routinely in every case (Wingo *et al.*, 1957).

Joint pains have been recorded in other published series. In one group of 43 patients 10 (23%) complained of joint pains, usually in the shoulders, elbows, and knees; in three cases they were severe enough to require the drug to be discontinued. These symptoms slowly disappeared in all patients after termination of treatment (Yeager *et al.*, 1952).

Another report on the combined use of pyrazinamide and isoniazid recorded joint pains in 10 (48%) of a series of 21 patients (Campagna *et al.*, 1954).

Cullen *et al.* (1956) treated 27 patients with pyrazinamide and isoniazid, and three of these developed clinical gout. One of the latter had a previous history of gout and another had a family history of gout. Cullen *et al.* were the first to show that the administration of pyrazinamide leads to hyperuricaemia, and elevated levels of serum uric acid were recorded in 26 out of the 27 patients. They also suggested that the concurrent administration of isoniazid would enhance this effect, and that of P.A.S. would reduce it. Similar results were obtained by Gleason *et al.* (1956). A number of papers on the subject were read at the Sixteenth Conference on the Chemotherapy of Tuberculosis.

Method

The serum uric acid levels of a

FIG. 1.—This and the following Graphs show the effect of pyrazinamide on serum uric acid and urinary uric acid. The effects of the addition of probenecid and aspirin (Shapiro and Hyde, 1957) are also illustrated.

FIG. 2

FIG. 3

FIG. 4

number of patients not receiving pyrazinamide were estimated, using a modified carbonate-phosphotungstate method (Henry *et al.*, 1957). In this laboratory 6.5 mg./100 ml. is regarded as the upper limit of normal for men. The uric acid content of a 24-hour specimen of urine was also measured by the same method, 400–700 mg. being regarded as the normal range of 24-hour excretion.

None of the patients in the untreated or pyrazinamide-treated group gave a previous history or family history of gout, and renal function was normal in each case.

Six patients on pyrazinamide in combination with one other drug were studied. In these cases this therapeutic regime had been started because of multiple resistance to the more commonly used drugs. In addition, two patients receiving a combination of streptomycin, P.A.S., and isoniazid were given pyrazinamide in place of P.A.S. and of isoniazid respectively for a brief period.

Pyrazinamide was administered in standard dosage of 2.5 g. a day. After a period of daily estimations of blood and urinary uric acid, in order to establish the degree of hyperuricaemia and associated diminished uric acid output in the urine probenecid in a dosage of 1.5 g. a day was added. In each case this led to a reduction in serum uric acid and an increase in urinary excretion of uric acid, although the values did not return to the normal range previously determined. The probenecid was not administered for long enough to confirm the suggestion (Kanner and Jacobs, 1957) that there is an "escape" from the effects of probenecid. In his cases, after a period of a few weeks on probenecid and pyrazinamide, the blood levels of uric acid returned to the range produced by pyrazinamide alone.

The accompanying Graphs of four patients are illustrative of the results obtained in all cases (Figs. 1–4).

A number of other patients on a regime including pyrazinamide were not studied in detail, but random serum uric acid levels revealed an elevation to an average of 9.2 mg./100 ml., with a concurrent reduction in urinary uric acid to an average of 195 mg. in 24 hours.

Conclusions

Pyrazinamide causes, within about 48 hours, a rise in serum uric acid and a reduction in urinary excretion of uric acid. Within a similar period of the suspension of this drug these figures revert to the normal range.

This effect was reduced by the concurrent administration of probenecid in standard dosage. In this series neither P.A.S. nor isoniazid was found to have any effect on the level of uric acid in the serum.

Pyrazinamide appears to act by interfering with the kidneys' ability to concentrate and excrete uric acid in the normal manner, presumably by increasing the tubular reabsorption of uric acid. It has been suggested that after prolonged pyrazinamide administration decreased urate excretion persists, this apparently also involving decreased production (Gleason *et al.*, 1956). This could be a physiological response to elevated serum uric acid levels, but may represent a more fundamental disturbance in urate metabolism.

It has been shown that the administration of pyrazinamide does not significantly alter the serum phosphorus level or the tubular reabsorption of phosphorus (Eisenberg and Mandel, 1958). The action of pyrazinamide on the renal tubular reabsorption mechanism may therefore be limited in its effect upon the uric acid. Pyrazin-

amide may thus be of use in the further study of the metabolism of uric acid and of gout.

Special care should be exercised in the use of pyrazinamide in patients with a past or family history of gout, as the development of hyperuricaemia may lead to the precipitation of clinical attacks of gout.

We are grateful to Miss Beryl Schumer, B.Sc., for carrying out the arduous biochemical investigations.

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HYPERURICAEMIA RELATED TO TREATMENT OF HYPERTENSION

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This paper surveys the serum urate levels and their relationship to drug treatment in 157 patients attending the hypertension clinic at Hammersmith Hospital. We were prompted to study hyperuricaemia in patients with hypertension for two reasons. Firstly, there is a known association between hypertension and gout, and, secondly, it has been demonstrated (Duncan and Dixon, 1960) that primary familial hyperuricaemia without gout may be associated with renal disease and hypertension.

Patients and Methods

All patients attending the hypertension clinic during a six-months period were admitted to this survey. These patients were suffering from essential or renal hypertension in either the benign or the malignant phase. Five patients who had attacks of gout were excluded. A total of 157 patients (86 women and 71 men) were

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