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. Pyrazinamide 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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studied, of whom 103 were receiving some form of drug treatment. The age range was from 21 to 85 years. The age and sex distribution in the treated and untreated groups was similar but the severity of the hypertension was not. 22 patients in the treated group (22%) had papilloedema (malignant hypertension) while only 6 (12%) in the untreated group had this severe form of the disease. These six patients were the cases of malignant hypertension diagnosed during the period of the study.

Simultaneous serum uric acid and serum urea estimations were made on each patient. Serum uric acid was estimated by a uricase method as modified by King and Wootton (1956). The accepted upper limit of normal with this method is 6 mg./100 ml. in males and 5 mg./100 ml. in females. Serum urea was estimated by the arsenic-diacetyl method (Rosenthal, 1955) and the normal upper and lower 10% limits are 35–16 mg./100 ml.

The drugs and doses in use in this clinic at the time of the survey were: pempidine, 5–100 mg. daily; mecamylamine, 5–80 mg. daily; pentolinium (oral) 200–800 mg. daily; reserpine, 0.3 mg. daily; chlorothiazide, 250–2,000 mg. daily. 45% of the treated patients were receiving a small dose of reserpine in addition to one of the ganglion-blocking drugs. Chlorothiazide was given alone in 10 patients and with ganglion-blocking drugs in 12.

Pempidine, mecamylamine, and chlorothiazide did not interfere with the estimation of either blood urea or serum uric acid.

Results

A large number of the treated patients had serum uric acid concentrations above the upper limit of normal. These data are summarized in Table I. Fig. 1 shows the distribution of serum uric acid levels in the 103 treated and 54 untreated patients. There is a skew of the distribution towards a higher proportion of raised values in the treated group; 32 patients (30%) in the treated group and 2 (4%) in the untreated group had a serum uric acid concentration above 7 mg./100 ml. Serum urea values were distributed similarly between the two groups (Fig. 2). The distribution of the serum uric acid levels with relation to the specific therapy is shown in Fig. 3. The 13 patients not included in this analysis were receiving multiple drug combinations.

TABLE I

Patients	Females with S.U.A. over 5 mg./100 ml.		Males with S.U.A. over 6 mg./100 ml.	
	No.	%	No.	%
Untreated ..	5	18·5	2	7·3
Treated	35	59	22	50

In 16 patients the serum uric acid was measured with and without the pressure-lowering drug. It was not justifiable to stop the drug treatment for this purpose, but where intercurrent illness or intolerance necessitated withdrawal, measurements were made. Results were also available in 10 patients starting treatment. In 14 of the 16 patients there was either an increase in the serum uric acid concentration when the drug was given or a fall on withdrawal (Table II). The increases observed with chlorothiazide were greater than with pempidine or mecamylamine.

Discussion

The number of patients with hyperuricaemia was much higher in the treated group than in the untreated group, though the values of blood urea were essentially similar. In both groups there was a higher proportion of elevated serum uric acid values among the patients with a high serum urea, but the association was not close.

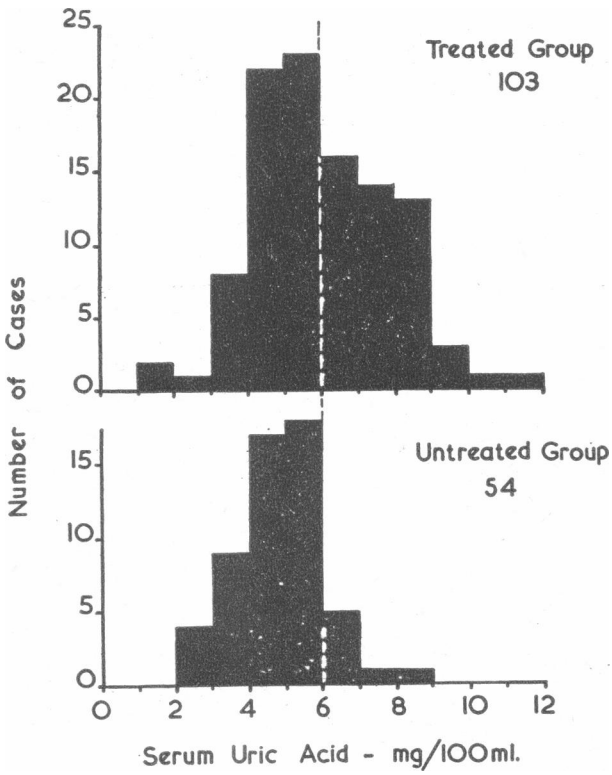

FIG. 1.—Distribution of serum uric acid values in 103 patients being treated for hypertension and 54 untreated hypertensive patients.

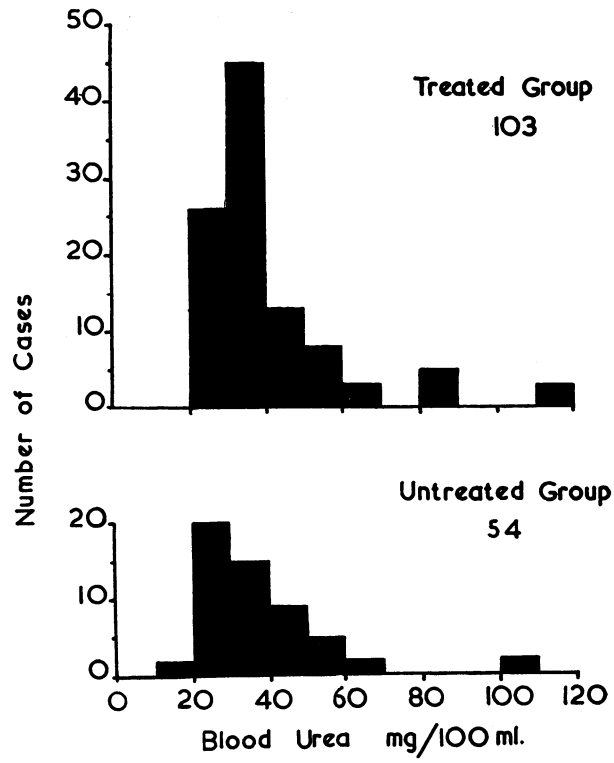

FIG. 2.—Distribution of serum urea values in the treated and untreated patients.

It seems that the antihypertensive drugs were responsible for the difference between the two groups. This interpretation was strengthened by the results in 16 patients studied during a change of treatment. 14 of them had a higher serum uric acid concentration when on the antihypertensive drug. The largest increases were observed in the patients having chlorothiazide and smaller increases with pempidine and mecamylamine. The highest proportion of elevated serum uric acid concentrations was found in the group having both chlorothiazide and pempidine or mecamylamine ; 10 out of 12 patients had a serum uric acid above 6 mg./100 ml.

The high incidence of hyperuricaemia related to treatment makes it impossible to derive any figure for the prevalence of primary hyperuricaemia among this group of hypertensive patients. 64 patients had a serum uric acid concentration above the upper limit of normal,

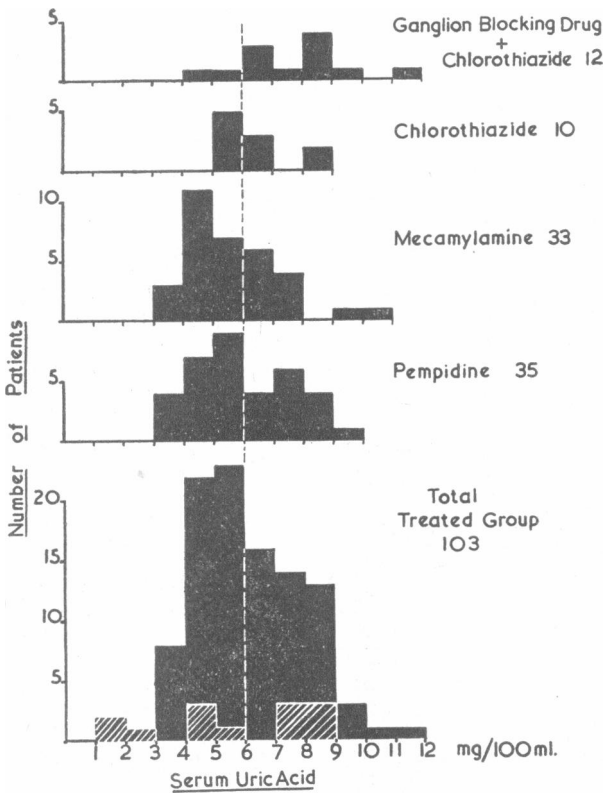

FIG. 3.—Serum uric acid concentrations separated into groups according to the drug treatment received—13 patients having multiple combinations have not been analysed separately (shaded areas).

TABLE II

Drug	Patient	Serum Uric Acid On Drug	Serum Uric Acid Off Drug
Chlorothiazide	1	8·1	5·1
	2	8·8	4·9
	3	7·5	5·8
	4	8·0	5·6
	5	6·4	5·0
	6	5·0	5·2
	7	5·7	4·5
Pempidine	8	6·0	3·4
	9	6·8	5·0
	10	9·9	6·2
	11	6·0	5·0
	12	5·2	6·0
	13	3·9	3·4
	14	7·9	5·9
	15	7·4	5·0
Mecamylamine ..	16	5·6	4·8

and it is possible that some of them had primary hyperuricaemia with resulting renal hypertension. Further study of untreated patients will be necessary to determine the incidence of this condition.

Hyperuricaemia caused by drugs has been described after treatment with pyrazinamide (Gleason *et al.*, 1956 ; Cullen *et al.*, 1957) and chlorothiazide (Laragh, 1958 ; Dinon *et al.*, 1958). It has not previously been recognized with blood-pressure-lowering drugs such as pempidine and mecamylamine. In our patients hyperuricaemia did not always occur and there was no clear correlation with drug dosage or level of blood-pressure. A reduction of the glomerular filtration rate, such as may occur when the blood-pressure is lowered, causes an increase in the concentration of serum uric acid, but the relationship between the serum uric acid and serum urea is complex. The serum uric acid rose steeply with only slight elevation of serum urea in patients having chlorothiazide. It is probable that much of the increase in serum uric acid observed with pempidine and mecamylamine was related to reduced renal blood flow which followed a fall in blood-pressure. A reduction in renal blood flow may not be the whole explanation, because the serum uric acid rose in some patients having pempidine without significant alteration in the serum urea.

It is important to recognize the possibility of a drug-induced hyperuricaemia for various reasons. Firstly, the correct diagnosis of an acute non-gouty arthritis may be confused if a high concentration of serum uric acid is found. Secondly, prolonged drug-induced hyperuricaemia may itself lead to clinical gout. We have observed the development of acute gouty arthritis in two patients who were having drug treatment for severe hypertension. One of these patients was having oral pentolinium and the other pempidine and chlorothiazide. Neither patient had any personal or family history of gout, and no measurements of serum uric acid were available prior to treatment. The attacks may have been coincidental or precipitated by the drugs without alteration in the serum uric acid. At the time of the attack the patient on pempidine and chlorothiazide had a serum uric acid of 16 mg./100 ml. with a normal blood urea.

It is possible that the prolonged hyperuricaemia which we have observed in our patients may cause or aggravate existing renal damage in the same way that patients with gout and primary hyperuricaemia may suffer progressive renal failure. Hypertensive patients who have drug treatment for years probably run a greater risk of developing gout from their hyperuricaemia than do patients who have induced hyperuricaemia for shorter periods of time, as may occur in patients with oedema who are given chlorothiazide. This danger can be assessed only by a long period of observation of serum uric acid concentrations and renal function.

Summary

Investigation of 54 untreated hypertensive patients showed that 18.5% of the females had a serum uric acid higher than 5 mg./100 ml. and 7.3% of the males had a serum uric acid concentration over 6 mg./100 ml. Among 103 hypertensive patients being treated with pempidine, mecamylamine, or chlorothiazide, 59% of the females had a serum uric acid over 5 mg./100 ml. and 50% of the males had a serum uric acid over 6 mg./100 ml. Fourteen patients out of 16 studied showed an elevation of the serum uric acid when they began

treatment with these drugs. The drugs themselves appear to be responsible for the elevation of the uric acid in the treated hypertensive patients.

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CONTROLLED DOUBLE-BLIND TRIAL OF "PERSANTIN" IN TREATMENT OF ANGINA PECTORIS

BY

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The long-acting coronary arterial vasodilator drugs in use at present are disappointing, and the frequent appearance of new drugs testifies to the ineffectiveness of most of them. Search continues for an efficient drug of low toxicity that will give symptomatic relief in angina of effort.

Recently a new preparation, 2,6-bis-(diethanolamine)-4,8-dipiperidine-pyrimido-(5, 4-d) pyrimidine ("persantin"), has been shown to increase the coronary arterial blood-flow in dogs to a greater extent (Kadatz, 1959) and to have a more prolonged action (Bretschneider *et al.*, 1959) than either papaverine or theophylline after intravenous injections. Encouraging clinical reports on a small number of patients with coronary arterial disease and anginal pain have been made (Pabst, 1959; Jünemann, 1959; Hamm *et al.*, 1959) but no controlled trial has been carried out.

We report here the results of a controlled "double-blind" trial of persantin in 30 patients with angina pectoris.

Present Investigation

Material and Methods.—Thirty patients with typical angina of effort who had previously been seen in the department were selected; all were in a "static phase." The severity of symptoms was assessed before treatment, and each patient was requested to note any side-effects and the time at which improvement, if any, occurred. Patients receiving glyceryl trinitrate were advised to continue to take this if necessary for symptomatic relief, but other long-acting vasodilators were stopped. The dose of persantin prescribed was two tablets (25 mg.) four times daily with a tablet of lactose identical in appearance as a control. The tablets were dispensed by the hospital pharmacist on a "double-blind" basis, and neither patient nor physicians knew which tablet the patient was receiving at any given time. Each substance was given for one month. Every patient was interviewed two weeks and four weeks after starting each course, when the standing blood-pressure was recorded and improvement or otherwise in the angina noted. Finally, the response during each four-week period was compared.

Results.—Five patients died suddenly during the trial, presumably from further coronary vascular episodes, and one patient defaulted. These six patients are therefore not included in the results. At the time of death two patients were receiving persantin and three the control tablet. The remaining 24 patients completed the trial. They fall into one of four groups as shown in the Table. Nine patients (37%) did not improve with

Effect of Persantin on 24 Patients with Angina

Improvement with persantin alone	4 (17%)
,, ,, control alone	1 (4%)
,, ,, both persantin and control	10 (42%)
No change	9 (37%)

either tablet; 10 (42%) improved with both tablets (6 received persantin first and 4 the control first); 4 (17%) improved with persantin alone, and 1 (4%) improved with the control. Side-effects were slight and consisted of mild headache in two patients and constipation in one while on persantin. One patient complained of mild dyspepsia while on the control tablet. The blood-pressure fell slightly in two patients while on persantin.

Discussion

Four patients improved with persantin alone but the improvement was only slight in two; one patient improved with the control tablet, and 10 patients improved with both tablets. Therefore 14 patients (58%) improved on persantin as compared with 11 (46%) on the control tablet. Improvement in many patients was only slight and in none was there a dramatic change. It is a common occurrence for preliminary reports of new drugs in treatment of angina to be encouraging and for such claims not to be substantiated in subsequent controlled trials. Persantin seems to be no exception to this, and under the conditions of this trial and in the dosage used it did not give significantly better results than a control tablet.

Summary

A controlled "double-blind" trial of persantin has been made in 30 patients with angina pectoris. Five patients died and one other did not complete the trial. In the remaining 24 persantin did not give significantly better results than a control tablet.

We thank Dr. A. Morgan Jones and Dr. E. G. Wade for advice and for allowing us to treat patients under their care, and Mr. J. B. Lloyd, chief pharmacist to the United Manchester Hospitals, for help in the organization of the trial. Messrs. Pfizer Ltd. supplied the persantin and control tablets.

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