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Hypertension and Hyperuricæmia

Stimulated by the suggestion that primary familial hyperuricæmia occurring without gout may cause renal disease and hypertension (Duncan & Dixon 1960), we have estimated the incidence of hyperuricæmia in patients attending Hammersmith Hospital hypertension clinic and attempted to find the mechanism of the raised serum uric acid. The association of hypertension with hyperuricæmia has been noted previously (Dollery *et al.* 1960, Kinsey *et al.* 1961, Itskovitz & Sellers 1962, Kölbel *et al.* 1965). In occlusive vascular disease affecting the heart (Gertler *et al.* 1951) or the brain (Hansen 1964), the incidence of hyperuricæmia is also many times greater than in the general population.

Patients, Methods and Results

All patients attending the hypertension clinic were admitted to the survey. The upper limit of normal of serum uric acid, which was measured by Folin's method adapted for the auto-analyser, was taken as 7 mg/100 ml for men and 6 mg/100 ml for women. Of 426 patients attending the clinic, 214 were men and 212 women; 140 men and 113 women (total 253, 60%) had a serum uric acid above normal limits; only 10 of these patients had gout.

Of 298 patients attending for the first time and not on hypotensive therapy, 153 were men and 145 women; 55 men and 37 women (total 92, 31%) had a raised serum uric acid. There were 106 men and 100 women with normal blood urea of whom 30 men and 24 women (total 54, 18%) had a serum uric acid above normal levels.

The severity of the hypertension in these patients, as assessed by the state of the ocular fundi (Keith *et al.* 1939) and by the level of the patient's diastolic blood pressure when first seen, is compared in Fig 1 with the severity of the hypertension in a group of patients with a normal serum uric acid. There is no significant difference between these two groups of patients as regards severity of hypertension.

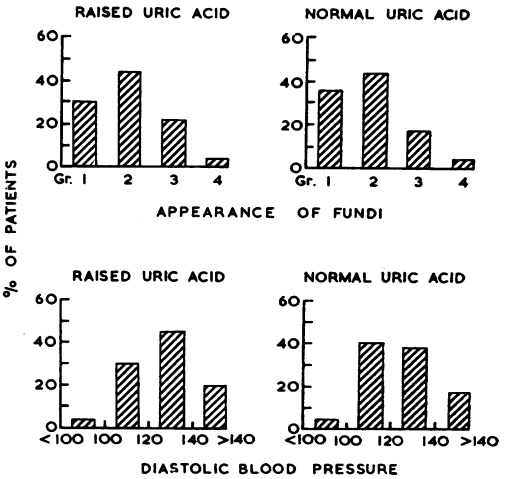

Fig 1 *Severity of hypertension and incidence of hyperuricæmia*

The renal handling of uric acid by 6 hypertensive hyperuricæmic patients has been compared with 5 hypertensive patients who have a normal serum uric acid (SUA) and with 6 subjects with a normal blood pressure (Table 1). Glomerular filtration rate (GFR) was measured by vitamin B_{12} clearance (Nelp *et al.* 1964, Breckenridge & Metcalfe-Gibson 1965), and uric acid clearance over two twenty-four-hour clearance periods. All patients were on a normal ward diet.

Finally, in 2 patients, uric acid pool size was estimated by the method of Sorensen (1960). In these 2 patients the uric acid pool size was 1,426 mg and 1,777 mg respectively, figures which are above accepted normal limits (upper limit of normal approximately 1,350 mg) (Sorensen 1960), while the corresponding uric acid turnover rates of 521 mg/24 h and 661 mg/24 h were within normal limits (upper limit of normal is approximately 950 mg/24 h) (Sorensen 1960).

Table 1
Hypertension and hyperuricæmia

Group	No. of patients	Mean SUA (mg/100 ml)	Mean GFR (ml/min)	Mean filtered load (mg/min)	UA clearance (ml/min)	UA excreted (mg/min)	UA clearance / GFR × 100
Normals	6	4·7	95·5	4·5	11·7	0·53	12·4
Hypertensive normo-uricæmic	5	4·7	81	3·8	8·8	0·42	11·2
Hypertensive hyperuricæmic	6	8·1	74	5·9	5·0	0·40	6·9

Discussion

There are several causes for the large number of patients with hyperuricæmia in the general survey of the clinic. Many had renal failure or were taking drugs known to cause a rise in serum uric acid – benzothiadiazine diuretics (Oren *et al.* 1958), rauwolfia alkaloids, or ganglion-blocking drugs (Dollery *et al.* 1960). It is of interest that neither methyldopa (Daley & Evans 1962) nor guanethidine (Fry & Barlow 1962) causes hyperuricæmia.

The incidence of hyperuricæmia in the 298 patients first attending the clinic, and with a blood urea below 40 mg/100 ml is 20%, or some three times the incidence in the general population (Popert & Hewitt 1962). There does not appear to be any correlation between the severity of the hypertension as indicated by the two measurements we have chosen, and the presence of hyperuricæmia, as has been suggested by Itskovitz & Sellers (1962).

There is an abnormality of renal handling of uric acid in those hypertensive patients who have a raised serum uric acid. As is shown in Table 1, the amount of uric acid filtered by this group of patients is greater than in the other two groups studied – 5·9 mg/min as compared with 4·5 mg/min in normotensive subjects and 3·8 mg/min in the group of hypertensive subjects who have a normal serum uric acid. The increased filtered uric acid load found in these hyperuricæmic patients does not correspond, however, with an increased uric acid clearance or an increase in the amount of uric acid excreted. This can be expressed in another way: the uric acid clearance expressed as a percentage of the glomerular filtration rate is only 6·9% in the hypertensive hyperuricæmic group, compared with 12·4% in the normal subjects and 11·2% in the other hypertensive patients. Thus the renal abnormality is not reduced glomerular filtration, but an abnormality at tubular level. The only other test of renal tubular function that we have performed is the ability of the kidney to concentrate urine, and 80% of the group of patients with hypertension and a raised serum uric acid can concentrate the urine to sp. gr. 1020, which we regard as satisfactory. A more precise delineation of this renal tubular abnormality is awaited.

Conclusions and Summary

Hyperuricæmia is common in patients with hypertension. Of 498 patients under treatment for hypertension, 60% had a raised serum uric acid; of 298 patients not on treatment and with a normal blood urea, 20% had a raised serum uric acid. The cause of the hyperuricæmia appears to be a defect in renal tubular handling. Uric acid pool size is increased in these patients, but the turnover rate is within normal limits; this supports the concept that there is a renal mechanism for the hyperuricæmia.

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Dr A P Hall (*London*): We have analysed the arterial blood pressure in 134 patients with primary gout at Hammersmith Hospital. Hypertension was arbitrarily defined in this context as a diastolic level of 100 or above in the majority of readings, and was considered 'severe' if antihypertensive therapy had been recommended by physicians in the hypertensive clinic.

The average age of the patients in the series was 59 years when last examined. The duration of follow-up is from one to twenty-five years, with a mean of five years.

Fig 1 is a histogram of the blood pressure levels of these patients when first seen (unhatched) and when last examined (hatched). Bearing in mind that 9% of the patients were receiving antihypertensive therapy there is little evidence of any rise in blood pressure over the period of follow up.

Eighty-eight of the 134 patients had a blood urea of 40 mg/100 ml or less, and of those patients 31 had hypertension, an incidence of 35%.

Visible tophi, obesity and proteinuria were more common in the hypertensive patients, but their fundi,

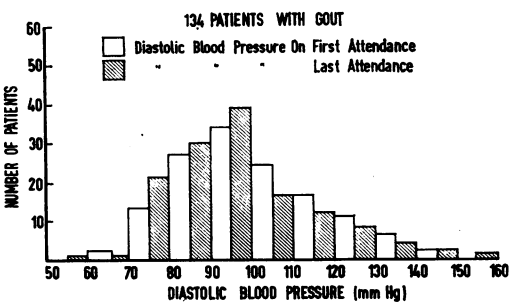

Fig 1 *Diastolic blood pressure in 134 patients with gout*

cardiac size and electrocardiograms were usually normal. Twenty-seven of those 31 patients did not require therapy. Of the 4 that did, 3 were obese and they responded quite satisfactorily.

Forty-six of the patients with primary gout had impaired renal function as judged by a blood urea of over 40 mg/100 ml, and of these 19 were hypertensive, an incidence of 41%, not significantly greater than the first group. But 8 of those 19 hypertensive patients did require antihypertensive therapy.

On the other hand, several of the patients with advanced renal failure showed no progression or even a fall in their blood pressure during the last few months or years of their disease. A striking feature is that 59% of the patients with impaired renal function did not have hypertension. One patient, who died of renal failure at the age of 32, remained normotensive throughout.

Hypertension and renal failure associated with gout appear to occur in two different forms, but admittedly with some overlap. The first and smaller group, exemplified by Duncan & Dixon's family (1960), show rapidly advancing renal failure, often at an early age, usually associated with severe and progressive hypertension, and the history of gout is frequently short. It is a reasonable hypothesis that the primary disease process in these patients is usually either some sort of renal lesion or hypertension, and that the hyperuricæmia and gout are secondary phenomena.

The second and larger group comprises patients with longstanding gout, who slowly develop renal failure, seldom develop severe or progressive hypertension, and whose life expectancy is often normal. For instance, one of our tophaceous patients now aged 82 developed gout in 1923. When first seen in 1953, his blood pressure was 250/110 and blood urea 49 mg/100 ml. His blood pressure in May 1965 had fallen to 150/90 and his blood urea has been virtually stationary over the last four years around 130 mg/100 ml.

This good prognosis in the majority of our patients is in accordance with Talbott & Lilienfeld's findings (1959) that the life expectancy in gout is not shortened. The overall incidence of hypertension in our series was 37%, an incidence similar to that found by Weiss & Segaloff (1959), and by Kuzell *et al.* (1955). The latter group found a higher incidence of hypertension in women, which is also our experience.

Our 10 women with gout have an average age – higher than the men's – of 70. Nine of the patients have a diastolic level of 100 or above, though only one of those patients required antihypertensive therapy. She died of renal failure, and it is possible that her gout was a secondary phenomenon.

The overall incidence of hypertension in gout is probably double that of the normal population of the same age, if the above figures are compared with the published figures of population surveys. In our clinical practice, however, severe or progressive hypertension is uncommon in primary gout.

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Dr C T Dollery (*London*): I think it may be unwise to draw too many general conclusions from the remarkable family that Duncan & Dixon investigated because I do not think we know exactly what was happening in them. I think that the explanation originally proposed, that they had hyperuricæmia leading to hypertension and to their early death, is unlikely to be the correct explanation in the light of Dr Hall's and other surveys of gout clinics. It does not look as though hyperuricæmia more than doubles the incidence of hypertension, if you allow for age and sex differences. In this family there seems to be a strange combination of the genes on one parent's side for hypertension and on the other side for hyperuricæmia, so that many of the children were afflicted by both these diseases. But geneticists seem unable to provide any satisfactory explanation of how this could have taken place with such a high incidence of both diseases in the children.

The next point I would like to mention is the great frequency of hyperuricæmia in our hypertension clinic – an incidence of 60%. This is very high, as we have taken a fairly high level, 7 mg/100 ml in men, as our upper limit of normal.

A final question I would like to put, is: What are the risks to these patients of having prolonged hyperuricæmia? When we begin to treat hypertension, it is likely that we shall go on doing so for the rest of the patient's days, and nowadays we are extending treatment of hypertension much further down the scale of severity. Many of our patients have, with treatment, quite a long life expectancy. May we expect to see a high incidence of gout in our patients after a decade or so of treatment? It does not look as though the risk can be large, because in the survey I did six years ago we found an incidence of hyperuricæmia very similar to that reported by Dr Breckenridge in his more extensive survey. Not many of these patients have developed clinical gout in the meantime, although some have.

Dr A St J Dixon (*London*): I would like to make a point about this family, which I agree is probably unique or almost unique. Since the publication of that report I have heard of three other similar families, but to my knowledge they have not been published, although I have seen quite extensive data on one family through the courtesy of Dr David Nicholson.

I do not really think that any one explanation, whether it be hyperuricæmia, inherited or secondary to other things, can explain all forms of gout. I noticed that Dr Hall used the term 'primary gout' and I understand the context in which he used it, but I am

sure he would agree that the cases brought together in this way really must be regarded as a miscellaneous collection of diseases.

Professor Sir John McMichael (*London*): So many people have seen this family, and *quot homines, tot sententiæ*. They have been extremely interesting, and when the two brothers died of malignant hypertension within weeks of one another we had a full clinico-pathological conference session on them. I think it is true that they were hyperuricæmic – that was recognized early – and some of them were only very mildly hyperuricæmic while they were in their teens. They became more hyperuricæmic as time went on. Their blood pressures did not go up until there were signs of progressive renal damage, and these two brothers who died certainly both had a streaky deposition of urate in their collecting tubules.

Dr B M Ansell (*Taplow*): In 1957 Professor Bywaters had a female patient in Hammersmith Hospital for investigation of gout beginning at the age of 22. Her third pregnancy was terminated and she was sterilized because of hypertension and incipient renal failure, so there are only two children. One of these, a girl aged 14, has recently presented with severe hyperuricæmia and some impairment of renal function, but without hypertension. The mother has done reasonably well on uricosuric therapy.

Dr J Seegmiller (*Bethesda, USA*): Dr A P Hall, in Boston, was involved in a project where a whole community, at Framingham, has been screened for a large number of biochemical and clinical abnormalities over the years as part of a cardiovascular research project. In 1965 he reported some data that seem pertinent to the discussion that we have had here. He has followed over these ten to fifteen years the patients who showed hyperuricæmia. A substantial portion of them have developed gouty arthritis, leading us to the view that perhaps the development of the arthritic manifestations that classify this condition as gout (and I think we should be clear on this distinction, in deference to the definitions that Garrod made) seemed to be a function of the degree of hyperuricæmia and the length of the exposure to hyperuricæmia.

He had some other data that were even more interesting and showed an increased incidence of myocardial infarctions among the hyperuricæmic group. When he separated the patients who had developed gout from those with essential hyperuricæmia, it was found that the increased incidence of myocardial infarction occurred primarily in the gouty group. This, of course, has considerable implications for the whole field of cardiovascular disease, and it really deserves to be corroborated with other such large-scale studies. It seems at variance with the papers that have already been quoted of Talbott, where patients with gout seem to have no diminished life expectancy. This sort of disagreement certainly must be resolved by additional work in the future.

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Population Studies of Serum Uric Acid

Epidemiological studies of gout have, until recent years, been restricted to family surveys, notably those by Scudamore in 1823 and by Talbott & Coombs in 1938.

Gout in Population Samples

Studies of gout in random population samples were first started in Leigh (Lancashire) by Kellgren and his colleagues in 1953. They found that 5 men and 1 woman gave a history which was consistent with a diagnosis of gout in the previous five years, giving a prevalence of 3 per 1,000 in men and 0·5 per 1,000 in women (Table 1). None was encountered in a rural sample of a thousand persons in Wensleydale (Yorkshire) examined by Popert & Hewitt (1962). In 1959 Decker & Lane compared Filipinos and non-Filipinos in a hospital population in the years 1954–9: of 25,645 male non-Filipino patients 34 (1·3 per 1,000) had gout compared with 7 of 281 male Filipinos (25 per 1,000). In 1960 Lennane *et al.*, in a comparison of Maori and non-Maori populations in Rotorua, New Zealand, found a prevalence of 42 per 1,000 in the Maoris but only 3 per 1,000 in those of European stock. There was thus a marked difference in the prevalence of gout between Polynesian and other Pacific populations and those of European stock.

Hyperuricæmia in Population Samples

In 1955 the results of population surveys, in which serum uric acid levels were estimated, began to be published. These presented a similar racial pattern. Curves for serum uric acid for a number of Caucasian male populations were constructed by Kellgren (1963). They all show a peak at between 4·5 and 5 mg/100 ml and an almost gaussian curve though with slight positive skew deviation. In the population of Wensleydale, examined by Popert & Hewitt (1962), the serum uric acid, estimated by the enzymatic method of Liddle *et al.* (1959) had a modal value of 3·5 mg/100 ml in women and 4·5 mg/100 ml in men. The frequency distribution of individuals aged 15–44 showed a gaussian curve in females but there was a positive skew in males. After the age of 55 the sex difference became less marked, the females having a modal value only 0·5 mg/100 ml less than the males but the curve in males had become bimodal, the large peak being as before at 4·5mg/100 ml, the smaller at 6 mg/100 ml. In Leigh, where only the 55–64 age group was examined by these authors, the modal value