GOUT AND HYPERURICAEMIA IN RURAL AND URBAN POPULATIONS

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Estimates of the prevalence of gout in different countries vary widely, but previously reported studies have related to selected groups, such as patients attending a hospital clinic, and no reliable information is available of the prevalence of the disease in the general population. Many well-authenticated reports have shown that the incidence of asymptomatic hyperuricaemia is in the region of 25 per cent. in the blood relatives of patients with gout (Talbot, 1940; Smyth, 1957; Stecher, Hersh, and Solomon, 1949). These studies have been interpreted as showing that hyperuricaemia is due to the inheritance of a single autosomal dominant gene with higher penetrance in the male than the female, although Hauge and Harvald (1955) suggested that more than one gene might be concerned. The familial nature of gout has been recognized since antiquity and is not in doubt, but whether familial hyperuricaemia is necessarily always associated with an increased incidence of clinical gout is not clear. Data bearing on this question, which have been obtained during surveys carried out by the Field Unit of the Empire Rheumatism Council under the direction of Dr. J. S. Lawrence, are presented in this paper.

Material and Methods

The prevalence of hyperuricaemia and gout has been estimated in an area sample of the population of Wensleydale. All individuals aged 15 years and over in the area had previously been examined clinically to estimate the prevalence of rheumatic complaints (Bremner, 1961). In the present survey a more detailed study has been made of an area sample which included half the main town of Hawes and half the villages and their surrounding farms in the Dale. There was a total of 485 males and 540 females aged 15 years and over in the sample (Lawrence, 1961). All respondents were examined clinically and radiologically and a blood sample was taken for serological and biochemical analysis; the overall completion rate was 87 per cent.

Wensleydale is a valley in the North Riding of Yorkshire lying 800 feet above sea level (for a detailed description, see Bremner, 1961). The inhabitants are mostly

engaged in sheep farming and dairying so there are no wide variations in dietary habits and general way of life.

An earlier survey of clinical gout and hyperuricaemia was carried out on a 1 in 10 random sample of the 55 to 64-year age group in the Lancashire town of Leigh. This sample consisted of 204 males and 277 females, of whom 173 males and 207 females were examined both clinically and radiologically, giving a completion rate of 79 per cent. (Kellgren and Lawrence, 1956). Leigh is an industrial town, the principal occupations of the male inhabitants being coal-mining and cotton-spinning, but as in the Wensleydale survey, the population is homogeneous with regard to diet and general way of life.

Method of Analysis.—In the Wensleydale survey serum uric acid was estimated by the enzymatic technique of Liddle, Seegmiller, and Laster (1959), using a commercial preparation of uricase.* Results were obtained on 436 males and 475 females from the total sample of 1,025 individuals, giving a completion rate of 89 per cent for the biochemical findings.

In the smaller Leigh survey, serum uric acid was estimated by the colorimetric technique of Henly (1958), using a phosphotungstic acid reagent. Some people refused to have a blood test and some of the blood samples were inadequate, so that results were obtained on only 136 males and 150 females, giving a completion rate of 60 per cent. for this part of the survey. Serial duplicate analyses were carried out in the majority of cases, except in the few instances when only a small blood sample was available.

57 sera covering the range of values found in these surveys were analysed in duplicate by both the enzymatic and colorimetric methods. A comparison of these results is shown in Fig. 1 (opposite). On average slightly higher values are obtained by the colorimetric technique; the arithmetical mean of these results is 4.4 mg./100 ml. by the colorimetric method and 3.9 mg./100 ml. by the enzymatic method. Therefore, these results differ slightly from the findings of Liddle and others (1959) who compared the present enzymatic technique with the colorimetric technique of Archibald (1957) and found that this colorimetric technique gave results which were on average 0.3 mg./100 ml. lower than those given by their enzymatic technique.

* Uricase Leo (E. Light & Co.).

Fig. 1.—Comparison of serum uric acid values obtained by the colorimetric technique of Henly (1958) and the enzymatic technique of Liddle, Seegmiller, and Laster (1959) in 57 estimations.

The mean values for the group obtained by each method are indicated by the broken lines. The unbroken line indicates 100 per cent agreement between the two techniques.

Results

In the Wensleydale Survey.—The distribution of serum uric acid levels by decade in the Wensleydale survey is given in Table I (overleaf) for both sexes. In males this distribution is relatively constant throughout the age groups studied, the mean values by decade showing little variation from the mean value of 4.5 mg./100 ml. calculated for the total male population. In females up to the age of 44 years, the mean values are about 1 mg./100 ml. lower than the corresponding values found in the males, *i.e.* 3.5 mg./100 ml. as compared with 4.5 mg./100 ml. However, a transition phase develops between 45 and 54 years so that the distribution of serum uric acid values in females begins to

approximate to that of the males. After the age of 55 years the mean values in females are only 0.5 mg./100 ml. less than the corresponding values found in males.

Since the distribution of serum uric acid in females is relatively constant between 15 and 44 years, and again after the age of 55 years the results for these age groups have been combined and compared with the corresponding male values (Figs 2 and 3, overleaf).

In the younger age groups, the modal value in males lies between 4.1 and 4.5 mg./100 ml., and in females between 3.1 and 3.5 mg./100 ml. Similarly, the actual range of values in males is greater, extending from 1.9 to 8.1 mg./100 ml. as compared with 1.9 to 6.1 mg./100 ml. in females. Both

TABLE I
DISTRIBUTION OF SERUM URIC ACID LEVELS BY DECADE IN WENSLEYDALE

Sex	Age Range (yrs)	No. of Persons	Distribution of Serum Uric Acid Levels by Decade (mg./100 ml.)															Mean Serum Uric Acid Level (mg./100 ml.)	Percentage of Persons with a Value Exceeding 6 mg./100 ml.	
			1-5	2	2-5	3	3-5	4	4-5	5	5-5	6	6-5	7	7-5	8	8-5			
Male	15-24	81	—	—	—	2	6	17	24	15	8	5	2	—	1	—	1	4.48	4.5	4.9
	25-34	61	—	1	1	2	2	8	14	18	6	4	3	2	—	—	—	4.63		8.2
	35-44	85	—	1	—	6	8	18	23	14	9	5	—	1	—	—	—	4.26		1.2
	45-54	87	—	—	1	5	5	16	21	19	11	4	2	2	1	—	—	4.48		6.9
	55-64	54	—	—	2	1	7	9	12	9	5	6	2	1	—	—	—	4.44	4.1	5.5
	65-74	43	—	—	—	—	5	10	11	8	2	6	—	—	1	—	—	4.46		2.3
	75+	25	—	—	—	1	—	3	8	7	3	2	1	—	—	—	—	4.65		4.0
Total	436	—	2	4	17	33	81	113	90	44	32	10	6	3	—	1	4.46	4.6		
Female	15-24	70	—	3	8	10	16	15	12	4	2	—	—	—	—	—	—	3.46	0.44	0
	25-34	70	—	1	5	15	24	13	5	5	1	—	1	—	—	—	—	3.41		1.4
	35-44	90	—	—	9	18	23	13	17	9	1	—	—	—	—	—	—	3.54		0
	45-54	75	—	1	1	13	21	16	9	7	5	1	1	—	—	—	—	3.76		1.3
	55-64	60	—	—	3	9	9	16	8	8	4	1	1	1	—	—	—	3.91	2.35	3.4
	65-74	77	—	1	5	7	9	16	18	13	5	2	—	1	—	—	—	4.00		1.3
	75+	33	—	—	1	4	3	7	12	2	2	1	1	—	—	—	—	4.09		3.0
Total	475	—	6	32	76	105	96	81	48	20	5	4	2	—	—	—	3.70	1.26		

curves show a slight positive skew, but this is more pronounced in males.

After the age of 55 years the modal value in males is unaltered, but in females it increases to 3-6 to 4 mg./100 ml.; there is now little difference in the actual range of values in males and females, 2-3 to 7-4 and 2 to 6-8 mg./100 ml. respectively. In females the skewed nature of the distribution curve is markedly increased, while in males the curve becomes slightly diphasic with a second peak between 5-6 and 6 mg./100 ml.

Taking the value 6 mg./100 ml. as an arbitrary upper limit of normal, "hyperuricaemia" was found in 24 males and seven females—an incidence of hyperuricaemia in this area sample of 5-5 per cent. for the total male population and 1-5 per cent. for the total female population. It is of interest that there was only one case of hyperuricaemia amongst pre-menopausal females, in which a serum uric acid value of 6-1 mg./100 ml. was found in a woman aged 29 years with a clinical history of toxæmia of pregnancy. It is very probable that this is an isolated instance of puerperal hyperuricaemia (Treadwell and Dixon, 1961), and hence in the present survey it is more useful to consider the prevalence of hyperuricaemia in females over 45 years of age (2-4 per cent.).

During the initial survey carried out by J. S. Lawrence in 1959, two individuals were recorded as suffering from slight clinical gout, but it was noted that neither gave a typical history of acute attacks or had unmistakable tophi.

One was a man aged 42 years who suffered from psoriasis and had chronic painful swelling of the great toes; the serum uric acid was 2-9 mg./100 ml., and in

retrospect it seems probable that this man had psoriatic arthropathy.

The second man, aged 72 years, had a small ulcerating nodule, which was thought to be a tophus, on his ear, and also clinical and radiological evidence of osteoarthritis in the hands, feet, and spine; the serum uric acid was 4-2 mg./100 ml., however, and uric acid crystals were not demonstrated in the nodule.

On reviewing the clinical findings (which were confirmed by one of us in 1960), together with the radiological and biochemical data, it seems improbable that either of these individuals was suffering from gout.

The 24 males and seven females with a raised serum uric acid level were reassessed for clinical gout in a follow-up study carried out by one of us (A.J.P.) in which special attention was paid to dietary habits. All blood relatives of the hyperuricaemic individuals within a 15-mile radius were also investigated, and x rays and a blood sample were taken from relatives not already included in the area sample.

The 31 hyperuricaemic individuals were found to belong to 25 families, and of the 161 living members, 100 were available for study, giving a total completion rate of 63 per cent.

Serum urea was estimated by the urease-nesslerization method (Varley, 1958) on all samples with a uric acid value of 6 mg./100 ml. or more, but only one elevated value (54 mg./100 ml.) was found in a male aged 81 years. Therefore it is unlikely that the raised uric acid values recorded were due to a generalized nitrogen retention.

The distribution of serum uric acid in the blood relatives of the hyperuricaemic individuals and in

Fig. 2.—Distribution of serum uric acid in the Wensleydale survey. 15 to 44-year age groups. The value 6 mg./100 ml., taken as an arbitrary upper limit of normal, is indicated by the broken line.

Fig. 3.—Distribution of serum uric acid in the Wensleydale survey. 55+ age groups. The value 6 mg./100 ml., taken as an arbitrary upper limit of normal, is indicated by the broken line.

their spouses is given in Table II. In neither instance did the mean serum uric acid and actual range of values differ significantly from the values calculated for the total area sample. One further case of hyperuricaemia was found in the group of relatives not included in the original survey, giving a total of 32 cases in the genetic study. Twelve of the 32 hyperuricaemic individuals were first-degree relatives in five families. Four other hyperuricaemic individuals had no relatives in the sample and in the remainder only a few of the known relatives were studied, so that the prevalence of a familial hyperuricaemia may have been greater than could be established from the available data.

Many of the hyperuricaemic individuals had some pain, stiffness, and limitation of motion affecting mainly the larger limb joints, but the clinical findings did not differ significantly from what might be expected in any sample of individuals of comparable age and sex; none had suffered from clinically recognizable gout.

Radiographs of the hands and feet were taken at the time of the survey and these were read independently by a second observer (J.H.K.) who was deliberately reading high so that any abnormal appearance that could possibly be attributed to gout was included. This observer recorded minimal radiological gout in ten instances and moderate changes in one. These films, together with all the films for the hyperuricaemic individuals plus films from an equal number of controls, were studied separately by one of us (A.J.P.) who had been making a special study of the radiological changes of gout; doubtful gouty changes or none were recorded in all except one film in which the changes were minimal: this film was recorded as doubtful by the other observer. Furthermore, the serum uric acid level was below 5 mg./100 ml. in all except

one of the individuals recorded as having radiological changes of gout. From this it may be concluded that no reliable radiological evidence of gout was found in this survey.

None of the relatives of the hyperuricaemic individuals showed any clinical evidence of gout. Radiographs of the hands and feet, together with control films, were read by the first observer and only one was recorded as showing slight gout: this film had previously been recorded as doubtful by the second observer. It may therefore be concluded that no clinical or definite radiological evidence of gout was found in the families of the hyperuricaemic individuals, although there was clear evidence of familial hyperuricaemia in twelve of them. In a previous clinical survey which included all the inhabitants of the Dale, Bremner (1961) reported only one case of gout; none was found among the 891 individuals seen in the area survey, and our results therefore confirm the rarity of the disease in this locality.

In the Leigh Survey.—The distribution of serum uric acid values in the smaller survey in Leigh is given in Table III (opposite). These results show a similar trend to that in Wensleydale, in that there is little difference between the mean values in males and females at this age. The absolute values are slightly higher than those found in Wensleydale, but this will be due in part to the different analytical techniques employed. For this reason also it is not possible to make a direct comparison between the two areas, but it is of interest that the trend of the frequency distribution curve is similar to that found in the older age groups in Wensleydale. In females the curve shows a marked positive skew, while in the males there is a slight diphasic distribution, the small second peak again lying between 5.6 and

TABLE II
DISTRIBUTION OF SERUM URIC ACID LEVELS IN THE RELATIVES AND SPOUSES
OF HYPERURICAEMIC INDIVIDUALS IN WENSLEYDALE

Relatives	Sex	Age (yrs)	No.	Range of Serum Uric Acid Levels (mg./100 ml.)	Mean Serum Uric Acid Levels (mg./100 ml.)	Mean Serum Uric Acid in Total Sample (mg./100 ml.)
Blood Relatives	Male	All	30	2.7-7.1	4.4	4.5
	Female	15-44	10	1.9-5.1	3.6	3.5
		55+	13	3.0-5.8	4.3	4.0
	Total		53			
Spouses	Male	All	4	4.4-6.1	5.2	4.5
	Female	15-44	6	2.3-5.1	3.45	3.5
		55+	8	2.1-6.1	4.2	4.0
	Total		18			

N.B.—One man and wife both hyperuricaemic (level 6.1 mg./100 ml. in each case).

TABLE III

DISTRIBUTION OF SERUM URIC ACID LEVELS IN THE 55 TO 64-YEAR AGE GROUPS BY SEX (LEIGH)

Sex	No. of Persons	Distribution of Serum Uric Acid Levels (mg./100 ml.)															Mean Serum Uric Acid Level (mg./100 ml.)	Percentage of Persons with a Value Exceeding 6.5 mg./100 ml.
		1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5		
Male	138	—	1	1	5	13	14	26	22	15	16	14	3	5	1	2	4.88	8.0
Female	150	1	—	2	14	23	28	26	23	13	9	6	2	3	—	—	4.29	3.35

6 mg./100 ml. To allow for the difference in the analytical technique used in this survey it is more useful to take 6.5 mg./100 ml. as an arbitrary upper limit of normal in estimating the incidence of hyperuricaemia; thus fourteen males and six females were hyperuricaemic, giving an incidence of 8 per cent. in males and 3.4 per cent. in females of this age group. When the test was repeated in 1959, using the enzymatic method, only eight of these individuals were found to be hyperuricaemic. Of the twenty individuals who were hyperuricaemic in 1954 (by the colorimetric method), eighteen were still available for study in 1959.

In the survey carried out by J. S. Lawrence and J. H. Kellgren in 1954 on a random sample of individuals in the 55 to 64-year age group, two males were recorded as suffering from possible clinical gout; when these men were re-examined in 1959 the diagnosis of gout was confirmed.

One man aged 67 years had had an attack of classical podagra as a young man, after tonsillectomy, and over the years had had three or four attacks a year, though these had been less severe since he suffered a stroke 3 years before. This man weighed 15 stone and had been over-weight for many years; he used to drink 15 pints of beer a week, though latterly he had reduced this to 2 or 3 pints; he was never a large eater of meat. Clinically there was osteo-arthritis in the right first metatarsophalangeal joint and nodular thickening of the right olecranon bursa. The serum uric acid level, which was 7.4 mg./100 ml. by the original colorimetric method, was 6.9 mg./100 ml. by the enzymatic method.

The second man, a builder's foreman aged 60 years, had had typical attacks of gout since the age of 55. He had always eaten much meat, and usually had four or five chops or $\frac{1}{2}$ lb. of steak for his dinner; he drank about 20 pints of beer a week. Clinically there was slight limitation of movement at the left first metatarsophalangeal joint, and there were several tophi on the ears: the serum uric acid level, previously 7.5 mg./100 ml. by the colorimetric method, was 8.1 mg./100 ml.

In 1959 one additional man was thought to show some clinical signs of gout.

This man, a retired labourer aged 70 years, had suddenly developed a painful swelling of the first interphalangeal joint of the right hand at the age of 62, and

this was followed by the development of similar swellings of several other proximal and terminal interphalangeal joints; there were two small deposits resembling tophi in the right ear. He had never eaten much meat, drank no beer, and had always been thin; the history was not typical of acute gouty arthritis, and clinically the diagnosis of gout was doubtful. The serum uric acid level, 7.4 mg./100 ml. in the 1954 survey by the colorimetric method, was still raised in 1959 (7.7 mg./100 ml. by the enzymatic method), but the serum urea was also raised (73 mg./100 ml.), and the possibility that the hyperuricaemia was due to renal failure cannot be excluded. There were radiological changes compatible with mild gout in the feet, but since there was also moderately severe osteo-arthritis, these are of doubtful significance.

The survey in Leigh carried out by J. S. Lawrence in 1954 was subsequently extended to include a 1 in 30 random sample of the whole population over the age of 15 years; a completion rate of 86 per cent. was achieved, but no further cases of clinical gout were discovered in the 1,343 individuals seen. Serum uric acid determinations were not done, but the second observer recorded slight gout in three radiographs, and moderate gout in one; none of these individuals had clinical evidence of gout.

Radiographs of the hands and feet of persons in the 55 to 64-year age group taken during the 1954 survey were read by the second observer; only six films were recorded as showing any evidence of gout, and all of these were scored as minimal. The original films of the hyperuricaemic individuals together with matched control films, were read independently by the first observer and five of the hyperuricaemic's films were scored as showing mild gout. Three of these were the individuals with definite or doubtful gout who have been described above. The other two both had radiological evidence of generalized osteo-arthritis and had no symptoms or signs of gout; the serum uric acid levels were 6 and 5.1 mg./100 ml. and it seems unlikely that either had gout.

Of the eighteen hyperuricaemic individuals who were studied in 1959, there were therefore two, or possibly three, with gout; none of the remaining fifteen had clinical or definite radiological evidence

of gout. With the exception of the man with presumed renal failure, the only individuals in whom hyperuricaemia and radiological evidence compatible with gout occurred together were the two in whom the diagnosis was certain clinically. The incidence of gout in the random sample of persons in the 55 to 64-year age group is therefore 1.3 per cent. in males and nil in females.

A study was then made of the available first degree relatives of the eight individuals who were still hyperuricaemic. Twenty of the 64 relatives were studied, the remainder being dead (26) or not available (18). The serum uric acid values in eighteen of these twenty relatives (Table IV) showed three further cases of hyperuricaemia. The mean value for the younger age groups in females does not differ from the mean value calculated for the corresponding age group in the Wensleydale area sample, but in the males and older age groups in females the mean values are distinctly raised when compared with the area sample.

TABLE IV

DISTRIBUTION OF SERUM URIC ACID LEVELS IN 18 RELATIVES OF HYPERURICAEMIC INDIVIDUALS (LEIGH)

Sex	Age (yrs)	No.	Range of Serum Uric Acid Levels (mg./100 ml.)	Mean Serum Uric Acid Levels (mg./100 ml.)
Male	All	6	1.5-8.1	5.1
Female	15-44	6	3.1-4.4	3.7
	55+	6	3.5-5.7	5.0

Of the two males with probable gout, one had five relatives all living abroad, but as far as he knew none had had any form of rheumatism.

The second had two brothers, both with undoubted gout: one brother, who was in hospital suffering from carcinoma of the pancreas, had had only two attacks in 7 years, had no clinical or radiological signs of gout, and had always taken an ordinary mixed diet with about one pint of beer daily; the other brother had had severe attacks in several sites about twice a year for 13 years, though the only clinical finding of note was thickening of the olecranon bursae. By contrast with the first brother, this man was obese, ate large quantities of poultry and fish, and drank at least a quart of beer daily. Two sisters had no evidence of gout. Of his two daughters, one had possibly had an attack in the big toe at the age of 40, but there was no clinical or radiological evidence of gout, and the serum uric acid was 4.4 mg./100 ml., although she ate large amounts of meat and other protein foods.

The male with possible gout had only one available

relative, a brother aged 70, who refused to co-operate in the survey.

The other five hyperuricaemics had thirteen relatives with no clinical or radiological evidence of gout, but two males had hyperuricaemic brothers (serum uric acid levels 6.2 and 6.6 mg./100 ml. by the enzymatic method).

Discussion

In Wensleydale no definite cases of gout were found among the 891 individuals seen in the area survey. In Leigh, two, or possibly three, cases of gout were found among the 380 individuals seen in the random sample of persons in the 55 to 64-year age group. No gout was found in the first-degree relatives of 32 individuals in Wensleydale who were hyperuricaemic, but five of the 25 families studied showed definite familial hyperuricaemia. In Leigh, two, or possibly three, cases of gout were found in the relatives of one hyperuricaemic individual who was suffering from gout, but none was found in the relatives of those with symptomless hyperuricaemia; familial hyperuricaemia was found in only three families, but other instances may possibly have been missed owing to the low completion rate of the family study in Leigh. Of the gouty family, two males (including the proband) were hyperuricaemic and the third may have been so before the onset of his terminal illness; the four female relatives were not hyperuricaemic. There does not appear to be any increase in the incidence of gout in the relatives of those with symptomless hyperuricaemia, and clinical gout only appeared more frequently when the proband was himself suffering from gout; it therefore seems probable that some factor other than, or additional to, the inheritance of hyperuricaemia is necessary for the production of gout.

Both primary gouty arthritis and gout occurring secondary to the chronic blood dyscrasias are characterized by a raised serum uric acid, but whereas in the latter instance the hyperuricaemia has been shown to be associated with the presence of giant cells in the bone marrow (Hickling, 1958) and results from the greatly increased turnover of nucleic acids (Yü, Weissmann, Sharney, Kupfer, and Gutman, 1956), the metabolic defect resulting in essential hyperuricaemia and its relation to primary gout is as yet unknown.

Since the elucidation of the metabolic pathways involved in purine biosynthesis, many studies have investigated the incorporation of isotopically labelled glycine into urinary uric acid in subjects with primary gout, and an overproduction of uric acid has been demonstrated in some, but not all, of the cases studied (Wyngaarden, 1957; Wyngaarden, Blair, and

Hilley, 1958; Seegmiller, Laster, and Liddle, 1958). Investigations by Sorensen (1959) have also indicated that a substantial degree of uricolysis occurs in man, giving rise to the possibility that some cases of hyperuricaemia may be due to a decreased rate of uricolysis. In a recent study, Seegmiller, Grayzel, Laster, and Liddle (1961) have assessed the incorporation of labelled glycine into urinary uric acid in gouty subjects and have attempted to correct for the extra-renal disposal of urate by the simultaneous administration of labelled uric acid. By this means they have shown that the degree of extra-renal disposal of uric acid varies widely in both normal subjects and gouty patients and actually masks an over-incorporation of glycine in the urinary uric acid of some patients. Despite the more refined technique, it has not been possible to detect overproduction of uric acid in all patients with primary gout, and this leads to the conclusion that, although this may be one cause of hyperuricaemia, other factors must operate.

One early theory implicated the kidney in the pathogenesis of gout by suggesting that the hyperuricaemia was a result of a decreased renal clearance of urate. This theory has been strongly criticized (Stetten, Talbott, Seegmiller, Wyngaarden, and Laster, 1957), but has more recently received support from the evidence that, if the serum uric acid levels of normal controls are raised to the levels found in patients with clinical gout, the controls achieve a much greater clearance of urate (Nugent and Tyler, 1959). Clinical gout is a rare finding in chronic renal impairment despite the presence of a concomitant hyperuricaemia, and it is generally assumed that the hyperuricaemia is not of sufficient duration or severity to precipitate acute arthritis. However, that a reduced renal clearance of uric acid can lead to hyperuricaemia and in some instances precipitate acute gout has been found with the antihypertensive drugs, such as chlorothiazide (Aronoff, 1960; Freeman and Duncan, 1960), and

also with pyrazinamide (Schneeweiss and Poole, 1960), which appear to act on the renal tubule and produce a retention of urate. It is perhaps unfortunate that the pre-treatment levels of serum uric acid were not known in the patients who experienced acute attacks of clinical gout on this therapy, since it is not possible to assess whether the clinical gout occurred *de novo* or was merely precipitated in individuals already predisposed.

Duncan and Dixon (1960) have suggested that chronic renal disease may result from hyperuricaemia in the absence of clinical gout, but the proband of the family they studied was in fact suffering from primary gout. Familial hyperuricaemia without gout was not associated with any obvious increase in the incidence of hypertension or toxæmia of pregnancy in our study, and a distinction should perhaps be drawn between simple familial hyperuricaemia on the one hand, and the familial hyperuricaemia of gouty families on the other.

The absence of gout among the 31 individuals in Wensleydale with some degree of hyperuricaemia is of interest. Although familial hyperuricaemia has in some instances been shown to result from an inherited metabolic defect (Emmerson, 1960), it seems likely that environmental factors may aggravate abnormalities produced by such defects. Hauge and Harvald (1955) found that clinical gout occurred in 15 per cent. of the hyperuricaemic relatives of patients with gout, and our results support the view that an abnormal diet is one of the principal factors determining the high incidence of gout in some hyperuricaemic families. The population of Wensleydale classified by social class is shown in Table V for comparison with the general population of England and Wales, patients attending the gout clinic of the Rheumatism Research Department of the Manchester Royal Infirmary, and a sample of consecutive out-patients attending the general rheumatism clinic at the Infirmary. It will be seen that amongst the gouty

TABLE V
SOCIAL CLASSES OF MALES

Sample		Total Number	Class Distribution (Percentages)					
			I-V	I	II	III	IV	V
England and Wales		12.5 million	100	3.5	15	53	15.5	13
Manchester Rheumatism Clinic	General	149	100	12	15	54	12	7
	Gout	95	100	30.5	30.5	30.5	7.5	1
Wensleydale	Total	461	100	1	53	19.5	23	3.5
	Hyperuricaemic ..	24	100	4	45.5	21	21	8.5

patients there is an excess of Social Classes I and II. In Wensleydale there is an excess of Class II, but this is mainly due to the large number of independent farmers in the Dale who in this marginal hill farming area are not especially prosperous. The actual occupations of the 95 gouty males from the clinic are also of interest, since this group contained 13 company directors, 10 managerial executives, 6 medical practitioners, 11 men from other professions, 10 salesmen, 7 men from the beer trade, 3 butchers, 3 grocers, and 2 fishmongers.

The diet of many patients attending the gout clinic was also unrepresentative of Britain as a whole, and was characterized by a high protein and low carbohydrate content and an average or high fat content. A high weekly consumption of beer was also frequent. By contrast the individuals with symptomless hyperuricaemia in Wensleydale and Leigh consumed an average diet with a considerable carbohydrate content and little beer. In this context it is interesting to note that, although there were 31 individuals in the Wensleydale sample with a serum uric acid level of 6 mg./100 ml. or more, the highest figure recorded was only 8.1 mg./100 ml., whereas much higher figures were often recorded in the gout clinic; it may be that the virtual absence of gout in Wensleydale is due to the fact that the hyperuricaemic families in this valley are not subjected to the dietary and other occupational hazards which were noted amongst the patients attending the gout clinic. This suggestion is supported by the observation that the diet of the gouty males in Leigh was somewhat different from that of the symptomless hyperuricaemics: thus one of these men was obese, habitually ate four or five chops or $\frac{1}{2}$ lb. of steak a day and drank 20 pints of beer a week. In the gouty family, two of three brothers with severe gout were obese and had high intakes of protein and beer, while the third, who had had only two attacks in all, had always been thin and abstemious; the four female relatives were not hyperuricaemic, but one, who had a higher protein intake than the others, had had one possible attack of gout. Gout was formerly known as the arthritis of the rich, and Brøchner-Mortensen (1958) noted that brewery workers, bar-tenders, salesmen, and professional men predominated among his patients; our experience is similar, and there seems little doubt that richness of the diet, if not financial richness, is a characteristic attribute of the patient with gout. Whether an inherited hyperuricaemia is a necessary predisposing factor remains uncertain, but our results suggest that the inheritance of hyperuricaemia does not necessarily determine the inheritance of gout.

Summary

The prevalence of hyperuricaemia and clinical gout have been estimated in an area sample of a rural population (Wensleydale) and a random sample of an urban population (Leigh).

The distribution of serum uric acid levels in these samples shows that in males the mean serum uric acid level remains constant throughout life, while in females lower values are found up to the time of the menopause. After the age of 50 years, the distribution in females begins to approximate to that found in males.

Despite a relatively high incidence of hyperuricaemia in both localities, no cases of clinical gout were found in Wensleydale, and only two definite cases were found in the Leigh sample. A follow-up study of the hyperuricaemic and gouty individuals together with their blood relatives revealed evidence of familial hyperuricaemia in eight of 33 families, but clinical gout was only seen in the relatives where the proband was already suffering from gout.

It is suggested that the inheritance of familial hyperuricaemia does not necessarily determine the inheritance of clinical gout, and that other factors, especially diet, may be concerned.

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La goutte et l'hyperuricémie dans des populations rurale et urbaine

RÉSUMÉ

On procéda à une enquête sur la fréquence de l'hyperuricémie et de la goutte clinique dans des échantillons d'une population rurale (Wensleydale) et d'une population urbaine (Leigh).

La distribution des taux d'acide urique sanguin dans ces échantillons montra que chez des hommes le chiffre moyen d'acide urique demeure constant pendant la vie, tandis que chez des femmes jusqu'au temps de la ménopause on trouve des valeurs plus basses. Après l'âge de 50 ans, la distribution parmi les femmes commence à se rapprocher à celle des hommes.

Malgré une fréquence relativement élevée de l'hyperuricémie dans les deux localités, on ne trouva pas de cas cliniques de goutte à Wensleydale et il n'y eut que

deux cas confirmés à Leigh. Des observations des sujets goutteux et hyperuricémiques et de leurs parents consanguins montrèrent l'existence d'une hyperuricémie familiale dans 8 sur 23 familles, mais la goutte clinique ne fut noté que chez des parents d'un goutteux confirmé de la série étudiée.

On pense que l'hérédité de l'hyperuricémie familiale ne détermine pas nécessairement l'hérédité de la goutte clinique et que d'autres facteurs, particulièrement le régime alimentaire, peuvent y jouer un rôle.

Gota e hiperuricemia en poblaciones rural y urbana

SUMARIO

La frecuencia de hiperuricemia y gota clínica fué investigada en muestras de una población rural (Wensleydale) y de una población urbana (Leigh).

La distribución de las cifras de ácido úrico sanguíneo en estas muestras probó que en hombres el nivel medio de ácido úrico permanece constante durante la vida, mientras que en mujeres se encuentran valores más bajos hasta el tiempo de la menopausia. Pasada la edad de 50 años, la distribución en mujeres comienza a aproximarse a la encontrada en varones.

A pesar de la relativamente alta incidencia de hiperuricemia en ambas localidades, no se encontraron casos clínicos de gota en Wensleydale y sólo dos casos ciertos fueron descubiertos en Leigh. Un detenido estudio de los individuos hiperuricémicos y gotosos junto con él de los consanguíneos reveló la evidencia de hiperuricemia familiar en 8 de 33 familias, pero gota clínica solamente fué vista en los familiares donde el miembro de la muestra sufría ya de gota.

Se sugiere que la herencia de hiperuricemia familiar no determina necesariamente la herencia de gota clínica y que otros factores, especialmente la dieta, pueden estar envueltos.