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Clinical survey of 354 patients with gout*

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Between the years 1958 and 1967, 354 patients with gout were examined personally at Hammersmith Hospital (257 cases seen between 1958 and 1967), and more recently at the Charing Cross and West London Hospitals (97 cases seen during 1966 and 1967). This paper describes a retrospective computer-assisted analysis of these patients. Some of them were followed for considerable periods of time by ourselves or our colleagues, whereas others were seen on one or two occasions only. The study does not therefore trace the course of the disorder over a period of time in individual patients.

Method

For the purpose of the survey gout was defined as recurrent acute episodes of arthritis in the presence of hyperuricaemia. Most of the serum urate values had been estimated with the use of the Technicon Auto-Analyzer; the upper limit of normal for serum uric acid was taken to be 6 mg./100 ml. for males and postmenopausal women and 5 mg./100 ml. for premenopausal women. These figures had previously been obtained by duplicate sampling with sera from the population survey of Popert and Hewitt (1962).

The presence of urate crystals in synovial fluid or of tophaceous changes was taken as confirming the diagnosis but these were not necessary criteria. The information for the survey was abstracted from the patients' case notes and recorded on a proforma with 100 slots which permitted 65 separate items of data to be assembled for each patient. These items were punched and fed into the Elliott computer at the Royal Postgraduate Medical School of London. Every item was cross-referenced with each of the others, thus demonstrating any association between one feature in relation to another.

Results

AGE AT ONSET

Symptoms were first seen between the second and ninth decades in both sexes. The distribution of the age at onset is shown in Fig. 1. The peak age at onset in men lay in the fifth decade, whereas in three-quarters of the women symptoms commenced after the age of 50 years.

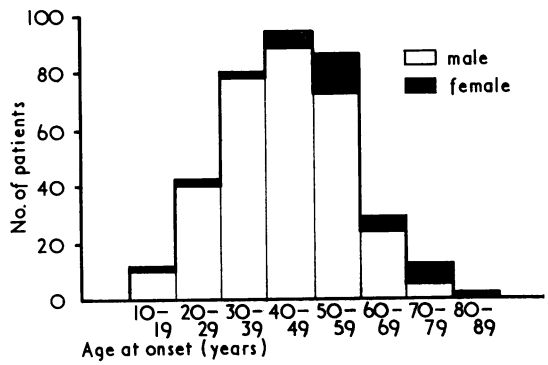

FIG. 1 *Age at onset in* 354 *patients.*

DURATION OF DISEASE

In 1967 when the survey was conducted the duration of disease was as shown in Fig. 2. Approximately half the patients were seen within 10 years of onset, the remainder at a longer interval.

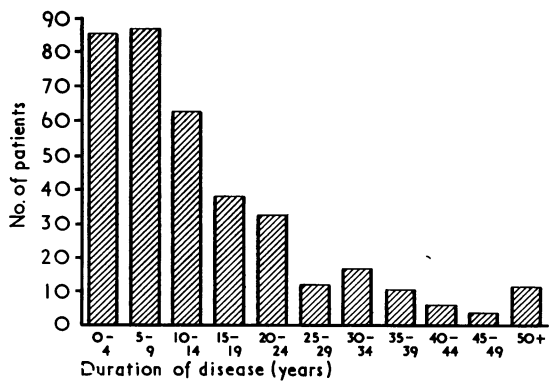

FIG. 2 *Duration of gout in* 354 *patients.*

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RACE

Of the 354 cases, 22 (6 per cent.) were non-caucasian subjects; these were all men, mostly Negroes with a few from India and the Far East, and they showed a significant tendency towards a younger age at onset ($P < 0{\cdot}01$), but this may have been because they belonged to a relatively young immigrant population. There were no other remarkable features about their gout.

SEX INCIDENCE

Of the 354 cases, 43 (9·7 per cent.) were women, and their gout differed from that seen in men in two important ways: the mean age at onset was higher (Fig. 1), and there was a higher incidence of renal involvement (see below).

SOCIAL STATUS

All male hospital patients were classified by occupation or profession according to the Registrar General's Classification of Occupations (1951).

For purposes of comparison a random selection of 200 non-gouty male controls attending the outpatient department were taken from the Medical Records of the Hammersmith Hospital and classified in the same manner. The result (Fig. 3) shows a significant preponderance of gouty subjects in the higher social classes ($P < 0{\cdot}002$). The 22 non-Caucasian subjects were of a significantly higher social class than whole series, because they included 12 subjects in Grade I from overseas, *e.g.* a cabinet minister from an African country and a maharajah.

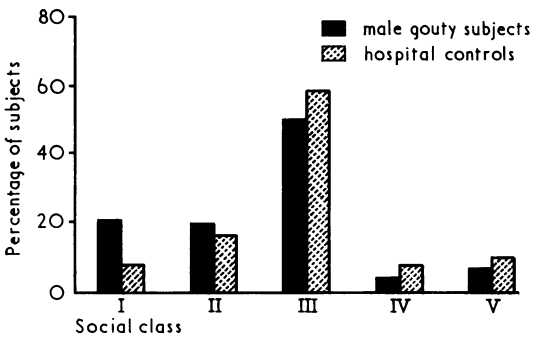

FIG. 3 *Social class of male gouty subjects compared with 200 hospital controls (Registrar-General's Classification). Note the excess of gouty subjects in the higher classes* ($P < 0{\cdot}002$).

FAMILY HISTORY

127 patients (36 per cent.) knew of at least one other member of their family who was said to have had gout.

OBESITY

169 patients (48 per cent.) were more than 15 per cent. above the ideal weight for their age and height (Society of Actuaries, 1959).

There were no other differences between these obese subjects and the remainder, except with regard to mild hypertension and alcohol ingestion (see below).

ALCOHOL

A patient consuming a minimum average daily intake of two pints of beer or two double whiskies was classified as a regular drinker. 130 patients out of the total series (37 per cent.) qualified for this grouping. Only 15 per cent. of the 34 women were drinkers and this sex difference was significant ($P < 0{\cdot}01$). There were 77 regular drinkers among 169 obese subjects (as defined above), compared with only 53 among 185 non-obese subjects, a significant difference ($P < 0{\cdot}01$).

JOINT INVOLVEMENT AND TOPHUS FORMATION

The incidence of past or present individual joint involvement was as follows (the individual categories not of course being mutually exclusive):

Joint	*Patients with individual joint involvement*	
	No.	*Per cent.*
Great toe	268	76
Ankle/foot	178	50
Knee	114	32
Finger	87	25
Elbow	35	10
Wrist	34	10
Other	14	4
Extra-articular gout (*i.e.* bursae, etc.)	10	3
More than one joint affected simultaneously	37	11
Permanent joint damage	60	17

Joint *x* rays were carried out in almost all cases and radiological evidence of tophi in juxta-articular areas was found in 127 (36 per cent.).

Subcutaneous tophi were clinically evident in 75 cases (21 per cent.).

Certain differences were observed in the individual pattern of joint involvement (see below) in relation to disease duration. Involvement of the great toe, ankle, fingers, and knees occurred irrespective of disease duration, but the incidence of wrist ($P < 0{\cdot}05$) and elbow ($P < 0{\cdot}05$) involvement was higher in patients with a longer duration. Furthermore, patients with elbow involvement tended to have an earlier age at onset ($P < 0{\cdot}01$).

Duration of disease and permanent joint damage were also related ($P < 0{\cdot}01$).

Of the 75 patients with clinical tophi, there were 33 (44 per cent.) with permanent joint damage, 15

(20 per cent.) with either elbow or wrist involvement, 27 (35 per cent.) with renal impairment, 21 (36 per cent.) with severe hypertension, and 19 (37 per cent.) with coronary artery disease (see below). All these constituted a significantly greater incidence than in the total group ($P < 0{\cdot}05$ in the case of renal failure; $P < 0{\cdot}01$ in the remainder.)

HYPERTENSION AND RENAL DISEASE

184 patients (52 per cent.) showed a diastolic blood pressure of 90 mm. Hg or more; in 31 of these it was 130 mm. Hg or more (designated "severe hypertension"); the remaining 153 (43 per cent.) were designated "moderate hypertension".

Renal failure was said to be present when a blood urea of more than 45 mg./100 ml. was found on any occasion, and occurred in 86 patients (25 per cent.).

The incidence of both moderate and severe hypertension was not related to duration of disease, indicating that there does not appear to be an increasing risk of developing hypertension with longer duration of gout (Fig. 4). Similarly, the incidence of renal failure showed no tendency to rise until the disease had been present for 40 years or more (Fig. 5). After this time the incidence approximately doubled, but these final decades of duration represent very old people and numbers are small. Otherwise there appears to be little if any deterioration in renal function with increased duration of disease.

With respect to age at onset, however, a different pattern was found. The incidence of moderate hypertension rose with increasing age at onset, but that of severe hypertension was highest in the decade 10 to 19 years (Fig. 6). In this group of 12 patients, 3 (25 per cent.) had severe hypertension. The incidence of renal failure related to age at onset showed a bimodal distribution curve (Fig. 7). It is apparent that there is a progressive rise in the incidence of renal failure as the age at onset rises from the fourth decade onwards; but there also appears to be a separate group in which disease begins in the second or third decade and in which there is a high incidence of renal failure.

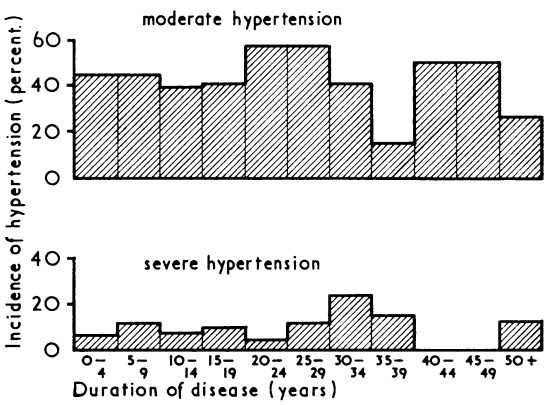

FIG. 4 *Incidence of hypertension related to duration of disease.*

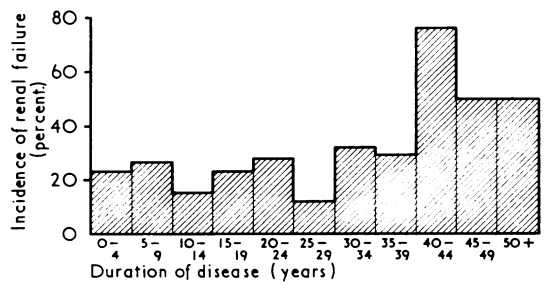

FIG. 5 *Incidence of renal failure (blood urea >45 mg. per cent.) related to duration of disease.*

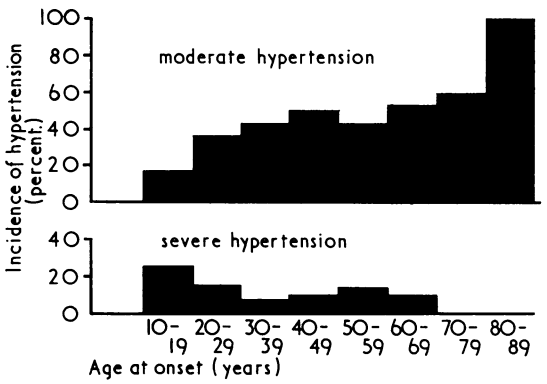

FIG. 6 *Incidence of hypertension related to age at onset.*

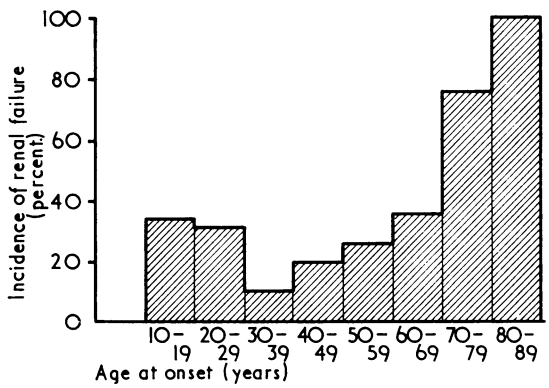

FIG. 7 *Incidence of renal failure (blood urea >45 mg. per cent.) related to age at onset.*

The incidence of renal failure in the group with severe hypertension was 16 out of 31, higher than that in those with moderate hypertension (39 out of 153) and normal tension (31 out of 170) ($P < 0{\cdot}05$).

In the group with severe hypertension there was a significantly greater incidence of permanent joint damage ($P < 0{\cdot}01$), tophus formation ($P < 0{\cdot}01$), and

X-ray changes ($P < 0.05$) than in the remainder, but this was not so in the moderate group. An association was also apparent between renal impairment and the presence of chronic tophi ($P < 0.01$).

In obese subjects the incidence of moderate hypertension was 84 out of 169, compared with 69 out of 185 non-obese subjects, a significant difference ($P < 0.01$). The incidence of severe hypertension (14 out of 169 obese subjects) was about the same as that in the non-obese group (17 out of 185).

Proteinuria was present in 77 cases (22 per cent.). There was no correlation with permanent joint damage, tophus formation, or duration of disease, but the incidence of proteinuria was significantly higher in patients with renal failure ($P < 0.01$).

A history of renal stones or renal colic was obtained from 32 patients (11 per cent.). Nine of these had passed stones of known uric acid composition. Stone formation correlated with the presence of renal impairment, proteinuria, and longer duration of disease.

Moderate hypertension was found in 18 of the 34 women (53 per cent.) compared with 119 of the 320 men (37 per cent.) ($P < 0.01$). Severe hypertension was found in 5 women (15 per cent.) compared with 26 men (8 per cent.) ($P < 0.05$).

Similarly, 19 of the women 34 (56 per cent.) showed renal impairment, compared with 67 of the 320 men (21 per cent.) ($P < 0.05$). In the whole series renal failure and hypertension were commoner in patients with a higher mean age at onset, and this may partially explain this sex difference.

OTHER FORMS OF VASCULAR DISEASE

The incidence of coronary artery disease, as evidenced by a history of myocardial infarction or angina, or by suggestive electrocardiogram changes, was found in 52 of the 354 patients (15 per cent.). A history indicative of cerebrovascular disease was obtained from 12 patients (3 per cent.) and 7 patients had other evidence of severe atheroma (*e.g.* affecting limb vessels). In the coronary group there was a high incidence of moderate (25 subjects) and severe (6 subjects) hypertension, and 22 had renal failure. These figures are significantly greater than in the rest of the series only in the case of renal failure ($P < 0.01$). There was also a high incidence of hypertension and renal failure in the very small number with cerebral or peripheral vascular disease.

SECONDARY GOUT

15 of the 354 cases (4·2 per cent.) had a known blood dyscrasia believed to be the main underlying cause of the hyperuricaemia and gout; these may be classified as follows:

Polycythaemia rubra vera	10
Polycythaemia due to cyanotic heart disease	1
Chronic myeloid leukaemia	1
Malignant lymphoma	1
Myelofibrosis	1
Congenital haemolytic anaemia	1

Most of these patients were referred by colleagues in the radiotherapy or haematology departments.

Secondary renal gout is often difficult to define because of multiple aetiological factors. There were eight patients in whom thiazide diuretics were considered to be contributory to hyperuricaemia and gout, but in none was the serum uric acid level quite normal when the drug was not being taken.

One patient developed gout for the first time while taking the antituberculous drug pyrazinamide. Serum levels of uric acid were very high but were controlled with uricosuric agents and he remained symptom-free. He was re-assessed after pyrazinamide had been discontinued and the uric acid level was found to be normal.

Five patients (described in detail elsewhere: Scott, Dixon, and Bywaters, 1964) had severe hyperuricaemia and gout associated with hyperparathyroidism.

One other man with gout and myxoedema has also already been discussed (Scott, 1966).

SERUM URIC ACID LEVELS

In each case the highest level recorded before treatment was taken for inclusion in the survey. The distribution pattern is shown in Fig. 8.

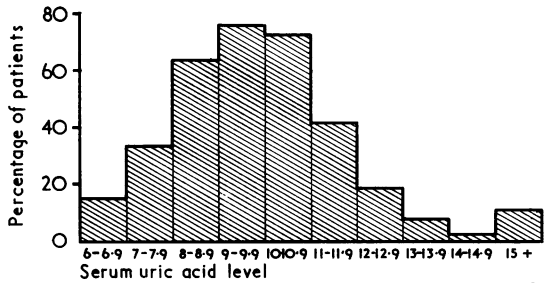

FIG. 8 *Pre-treatment serum uric acid levels, mostly estimated by Technicon Auto-Analyzer method. Upper limit of normal* 6 *mg. per cent. for males and post-menopausal women, and* 5 *mg. per cent. for pre-menopausal women. (Duplicate sampling with sera from Manchester population survey (Popert and Hewitt,* 1962)).

Patients showing chronic joint change and also those with gout secondary to a blood dyscrasia gave significantly higher serum levels of uric acid than the remainder ($P < 0.01$ and $P < 0.05$ respectively). Apart from this the level of uric acid before treatment did not correlate with any of the other features investigated, *e.g.* tophus formation or duration of disease.

URIC ACID EXCRETION

This was measured over one or more 24-hour periods in 89 patients, who had taken a low purine diet* for about 5 days previously to minimize the effect of dietary purines.

In order to determine whether or not the daily quantity of uric acid excreted was associated in any way with the clinical pattern of disease, 56 patients in whom the 24-hour urinary excretion exceeded 600 mg. were compared with the other 33 in whom the excretion rate was less than this.

No difference was found between these two groups with regard to any of the features examined (except that three patients with a blood dyscrasia whose 24-hour excretion was measured were all found to excrete high quantities of urate). Only three of the nine patients known to have passed a uric acid stone had their urinary urate excretion measured: two of them had high levels. One patient excreting a high level of uric acid also had epilepsy and mental retardation; he was found to have a partial deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase, and his case has been presented in full elsewhere (Bluestone, 1968).

TREATMENT

At some time in their previous history 174 patients (49 per cent.) had received probenecid and 30 (8 per cent.) sulphinpyrazone, while 112 (32 per cent.) had been treated with allopurinol. Complications—usually dyspepsia or skin rashes—were seen in 9 patients on probenecid,† 5 on sulphinpyrazone, and 3 on allopurinol.

Acute attacks of gout supervening within 3 months of starting long-term therapy occurred in 14 patients on probenecid, 1 on sulphinpyrazone, and 17 on allopurinol. The last group showed a greater liability to develop acute gouty arthritis than the uricosuric group ($P < 0.05$).

DEATHS

At the time of the survey 31 of the 354 patients had died while in hospital, from the following causes:

Carcinoma	5
Myocardial infarction	8
Malignant hypertension and uraemia	4
Rheumatic or congenital valvular heart disease	2
Amyloid	1
Cerebral haemorrhage	1
Cirrhosis	1
Septicaemia	1
Congenital haemolytic anaemia	1
Nephrotic syndrome	1
Chronic nephritis	1
Myelosclerosis	1
Pulmonary embolus	1

*NIH Bethesda low purine diet, containing about 200 mg. purine daily.
†This also includes two patients who developed nephrotic syndrome while taking probenecid (Scott and O'Brien, 1968).

Discussion

Several large series of patients with gout have been recorded during the last 150 years (reviewed by Copeman, 1964: Talbott, 1967). A retrospective study of this type must present certain unsatisfactory features. In the first place it must be remembered that, although some of the patients in the survey have been the subject of various published studies, many were seen on a consultative service basis only. Investigation was therefore often minimal. Secondly, it is now well recognized that many factors may cause or contribute to hyperuricaemia (Scott, 1969) and thus to gout, which cannot therefore be regarded as an aetiological entity. Nevertheless the many points of similarity demonstrated in this study between gouty subjects excreting more or less than 600 mg. uric acid daily emphasize the general clinical homogeneity of the condition as it presents itself to the physician. Obvious exceptions to this include overproducers of uric acid who form renal calculi, cases of gout complicating myeloproliferative disorders or advanced renal failure, and subjects with the Lesch-Nyhan syndrome (Lesch and Nyhan, 1964).

Our finding that in males the peak age at onset lies in the fifth decade is in conformity with most other surveys conducted during the 20th century (Futcher, 1915; Brøchner-Mortensen, 1941; Barceló, Sans-Sold, Santamaría, and Obach Benach, 1967). By contrast, in 19th century studies, the peak in males was one decade earlier (Scudamore, 1823; Strandgaard, 1899). The reason for this discrepancy is not certain but could be explained on the basis of an increasing life-expectancy over the past 150 years.

In women the peak age at onset lies in the sixth decade, and this no doubt reflects the physiological rise in the level of serum urate that occurs in women after the menopause (Mikkelsen, Dodge, and Valkenburg, 1965).

The percentage of women in the present study is higher than in almost all other surveys in which the incidence ranged from 2·7 per cent. (Barceló and others, 1967) to 7·9 per cent. (Schnitker and Richter, 1936). The finding of a female incidence of 26 per cent. by Kuzell, Schaffarzick, Naugler, Koets, Mankle, Brown, and Champlin (1955) is exceptionally high and certainly does not conform to common experience.

It has been a distinct clinical impression since the time of Sydenham (1717) that gout affects the rich more than the poor. Popert and Hewitt (1962) showed that there was an excess of individuals in the Registrar General's Social Classes I and II among gouty patients compared with patients attending a general rheumatology clinic. The present study

confirms this finding. Though gout clearly occurs in all socio-economic classes there was a significant bias towards the higher classes among the gouty men. This is compatible with the finding of higher serum uric acid levels in business executives than in craftsmen (Dunn, Brooks, Mausner, Rodnan, and Cobb, 1963; Montoye, Faulkner, Dodge, Mikkelsen, Willis, and Block 1967).

The familial tendency of gout has been known since classical times from the writings of Galen and Seneca. Our finding that 36 per cent. of our gouty patients knew of at least one other member of their family similarly affected is in general accord with previous series in which the incidence ranged from 10 per cent. (Brøchner-Mortensen, 1941) to 89 per cent. (Barceló and others, 1967). Similarly, the association between gout and obesity has previously been well-documented (Williamson, 1920; Brøchner-Mortensen, 1941). Defining obesity as any weight in excess of 15 per cent. above the Ideal Weight, we find that the incidence among our gouty patients is 48 per cent. Many patients with gout are regular drinkers (37 per cent. in the present series), and this association too has been noted in the past (Williamson, 1920; Brøchner-Mortensen, 1941). It has been established that acute alcoholic intoxication provokes hyperuricaemia by means of lactic acidaemia (Lieber, Jones, LoSowsky, and Davidson, 1962), but the relationship between this phenomenon and hyperuricaemia in habitual chronic alcohol ingestion is not clear.

The various factors which govern the association of hyperuricaemia, gout, renal disease, and hypertension are as yet ill-defined and causal relationships are difficult to establish. It has been stated that renal failure is the most frequent cause of death in patients with gout (Talbott and Terplan, 1960). This has to be reconciled with the finding of Talbott and Lilienfeld (1959) that life expectancy is not materially reduced in patients with gout; of the 31 patients who died in the present series, 8 died of myocardial infarction and this was the most common single cause of death.

It is true that we have information concerning only those patients who died while in hospital, and a number of others have probably died elsewhere of causes unknown to us. However, the available figures do not indicate a preponderance of renal causes for death.

The occurrence of renal disease in primary gout has been studied in recent years by Gonick, Rubini, Gleason, and Sommers (1965) and by Barlow and Beilin (1968); the latter authors examined 53 gouty patients and confirmed the frequent occurrence of hypertension, renal insufficiency, urolithiasis, and obesity. There are also several reports indicating that the serum uric acid level tends to be raised in patients with essential hypertension. Thus Breckenridge (1966) found an incidence of 27 per cent.; in these subjects the filtered load of uric acid was higher than in normouricaemic patients, but urate clearance was lower, indicating a tubular defect of uric acid excretion.

A high incidence of hypertension and renal failure was found in the subjects of the present study. It is of interest that no correlation could be found between hypertension and duration of disease until gout had been present for 40 years or more, when the increased incidence referred to a small number of very old people. It may therefore be inferred that there is in general little deterioration in renal function with increased duration of disease; the possibility remains, however, that a process of selection was operating, in that the patients with disease of long duration were those with a benign prognosis in whom blood pressure and renal function had not deteriorated and who had therefore survived. This question could be finally settled only by a prospective study in which the progress of untreated gouty patients was compared with that of a control group, a situation unlikely ever to occur.

This situation may be contrasted with the relation to age at onset. The incidence of moderate hypertension rose with increasing age at onset, but severe hypertension was *relatively* commoner in the young. Again, although there was a progressive rise in the incidence of renal failure with rising age at onset after the fourth decade, there was a relatively high incidence in the second and third decades. These findings emphasize the heterogeneity of our population and indicate the existence of a separate group of young subjects with gout and severe hypertension and/or renal failure. It may be pointed out, however, that these patients presented, in the first instance, with the symptoms of gout, and not with those of renal or vascular disease; although these soon followed. The existence of these two groups is in conformity with a previous analysis of some of these patients (Hall, 1966) and is consistent with the good prognosis found in most patients by Talbott and Lilienfeld (1959).

It has been shown that there is a correlation between urinary urate excretion and uric acid turnover rate (Scott, Holloway, Glass, and Arnot, 1969), so that a high excretion is an index of overproduction. It has been demonstrated that, on a purine-free diet, 21 to 28 per cent. of gouty patients excrete more than 600 mg. uric acid per 24 hrs. (Gutman, Yü, and Berger, 1959; Seegmiller, Grayzel, Laster, and Liddle, 1961). The much higher incidence in this series (63 per cent. of 89 patients tested) is no doubt to be explained by the more generous allowance of purine in the diet used. No difference could be found between the subjects producing large amounts of

uric acid and the others; it is known that urinary urate excretion tends to be high in patients with uric acid calculi (Gutman and Yü, 1968), but the number of such patients in the present study was too small to analyse.

In only 4·5 per cent. of the gouty patients was there an underlying myeloproliferative disorder. Many of these patients were referred by Departments of Radiotherapy and Haematology specializing in the treatment of these disorders, so that the true incidence is almost certainly lower. In the series reported by Yü (1965), it was 3·7 per cent.

The present study did not attempt to assess the effect of long-term therapy aimed at lowering the level of serum urate. It was, however, established that the occurrence of acute gout within 3 months of the institution of such therapy was significantly higher in those receiving allopurinol than in those receiving the uricosuric drugs.

Summary

A computer-assisted analysis has been carried out on 354 patients with gout, all seen personally between 1958 and 1967.

The peak age at onset lay in the fifth decade in men and in the sixth decade in women. The series included 34 women (9·7 per cent.). There were significantly more members of the higher social classes than in a control group of out-patient attenders. 127 patients (36 per cent.) gave a family history of gout.

169 patients (48 per cent.) had body weights which lay more than 15 per cent. above their ideal weight and 130 (37 per cent.) of the patients were classified as regular alcohol drinkers.

The pattern of joint involvement was analysed. Subcutaneous tophi were present in 75 patients (21 per cent.).

184 patients (52 per cent.) had a diastolic blood pressure of 90 mm. Hg or more; 31 (9 per cent.) of these had severe hypertension with a blood pressure of 130 mm. Hg or more, the remaining 153 (43 per cent.) being designated as cases of moderate hypertension. A blood urea of more than 45 mg./100 ml. was observed in 86 patients (25 per cent.). The incidence of both mild and severe hypertension was not related to duration of disease. Similarly, the incidence of renal failure did not rise until the disease had been present for over 40 years. In contrast, although the incidence of moderate hypertension rose with increasing age at onset, severe hypertension and renal failure were relatively common in a group of young subjects.

In 15 patients (4·2 per cent.) gout was believed to be secondary to a known blood dyscrasia.

No difference in the clinical pattern of gout could be observed between subjects excreting large or small amounts of urinary uric acid, although the number of patients with uric acid calculi was too small for analysis in this respect.

We should like to express our gratitude to the staff of the Computer Centre, Royal Postgraduate Medical School, and to the Records Department of Hammersmith, West London, and Charing Cross Hospitals, for their invaluable assistance.

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