

JOINT COMPLAINTS IN POLYCYTHAEMIA VERA*

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The reported incidence of gout and hyperuricaemia in polycythaemia vera has varied in different series. Thus Tinney, Polley, Hall, and Giffin (1945) reported clinical gout in 4.7 per cent. of 168 cases, Videbaek (1950) in 9 per cent. of 125 cases, and Lawrence, Berlin, and Huff (1953) in 7 per cent. of 159 patients, and unspecified arthritis in a further 14 per cent. On the other hand, Wasserman (1954) found gout in only 1.9 per cent. of 270 patients. The frequency of hyperuricaemia is less well documented, but Stroebel and Law (1956) noted its occurrence in 28 per cent. of patients with polycythaemia vera and a normal peripheral white blood cell count, and in 54 per cent. of patients with a myeloid immaturity.

The present paper reports the incidence of joint complaints and hyperuricaemia in an unselected group of patients suffering from polycythaemia vera.

Material

All the patients with polycythaemia vera who attended the Radiotherapy Department at Hammersmith Hospital during the 12-month period October 1, 1961, to September 30, 1962, were reviewed. The majority had received treatment for their disease before the commencement of the investigation. The diagnosis of the condition had been made on the basis of a red cell volume estimation (R.C.V. greater than 35 ml./kg.), peripheral blood count, and bone marrow puncture. In the group with a normal leucocyte and platelet count, secondary polycythaemia was excluded as far as possible by a number of accessory investigations (Szur, Lewis, and Goolden, 1959).

Of 101 patients reviewed, fourteen could be considered to belong to the thrombocythaemic group as they initially presented with platelet counts of 1,000,000 or over and the majority showed the tendency to repeated haemorrhages characteristic of this group. Eight of the 101 patients had developed myelosclerosis as confirmed by bone biopsy, either after therapy with ³²P (radioactive

phosphorus) or in the natural course of the disease. In the latter, the existence of polycythaemia vera was well established in the past (Szur and Goolden, 1960).

Ninety of the 101 patients had received treatment with ³²P on one or more occasions in the past, but none had been treated in the 3 months before this survey.

The disease was considered to be in haematological relapse when the packed cell volume was above 50 per cent., or when the platelet count was 1,000,000 or over in the thrombocythaemic group. By these criteria, 54 of the 101 patients were considered to have "active" disease, whilst 47 were in the stage of haematological remission.

During the course of the survey, two of the patients were found to have hypernephroma and one polycystic disease of the kidneys. In one of them, the increase in red cell mass was almost certainly related causally to the kidney lesion as he had only erythrocytosis with a normal platelet and leucocyte count, and without splenomegaly: the renal lesion, however, was not obvious at the start of the survey. In the other two the association was a much more doubtful one.

Method

The purpose of the survey was explained to the patients, who were interviewed about a personal or family history of rheumatic complaints and specifically of gout, after which the musculo-skeletal system was examined. Whenever possible, a sample of blood was obtained on which a full blood count, serum urea (standard technique for use on the auto-analyser), uric acid (Caraway's method modified for use on an auto-analyser, 1955), and differential agglutination test (D.A.T.: Rose, Ragan, Pearce, and Lipman, 1948) and latex-fixation test (Singer and Plotz, 1956) were performed. A radiograph of the feet was taken routinely and of other joints as indicated by symptoms.

Results

All the 101 patients available co-operated fully in the clinical assessment. Adequate blood samples were available for blood counts, D.A.T., and latex test in all of them and for uric acid and urea estimations in 99 patients. Radiographs of the feet were

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taken in 94 patients. The age and sex distribution at the time of the survey is shown in Table I.

TABLE I
AGE AND SEX DISTRIBUTION IN 101 CASES OF
POLYCYTHAEMIA VERA

Age (yrs)	Male	Female	Total
25-34	1	1	2
-44	5	1	6
-54	10	7	17
-64	21	15	36
-74	12	14	26
75+	8	6	14
Total	57	44	101

A family history of gout was obtained from three patients, two male and one female, involving the maternal grandfather of both male patients and the mother of the female patient. Only one of these three, a male, gave a personal history of gout, and this was confirmed radiologically.

Incidence of Gout and Other Forms of Arthritis

A clinical diagnosis of gout was made when there was a clear-cut story of a single or recurrent acute attacks of pain, redness, and swelling of one or more joints. This occurred in fourteen patients, nine males and five females. In twelve, the symptoms were confined to one or both great toes; in one the toes, feet, knees, and elbows were involved, and in one the metacarpophalangeal joints were affected initially, and later the elbows. In five patients, the first attack of gouty arthritis preceded the diagnosis of polycythaemia by 1 to 10 years.

At the time of the survey, inflammatory polyarthritis was present in three males, in two of whom it was associated with psoriasis, and in two females, both of whom had a family history of rheumatoid arthritis and were thought to be suffering from that disorder. A past history of polyarthritis was given by three males and two females. In two of the males this had been diagnosed as rheumatic fever at the age of 9 and 15 years respectively, while the third had had an acute episode of polyarthritis of undetermined type 1 year previously. One of the females had a history compatible with rheumatic fever at the age of 20 while the other had suffered two acute episodes of polyarthritis compatible with mild rheumatoid arthritis and showed erosive changes radiologically.

Degenerative joint disease of the first metatarsophalangeal joint was diagnosed clinically in ten males and fifteen females on the basis of detectable bony enlargement of the joint in the absence of a history suggestive of gout. Degenerative joint disease at

other sites was found in nine males and eight females. (Table II).

TABLE II
RHEUMATOLOGICAL MANIFESTATIONS IN
101 PATIENTS WITH POLYCYTHAEMIA VERA

Clinical Diagnosis	Male	Female	Total
Gout	9	5	14
Inflammatory Polyarthritis ..	3	2	5
Past Polyarthritis	3	2	5
Degenerative Joint Disease			
First metatarsophalangeal	10	15	25
Other sites	9	8	17
Total	34	32	66

Serum Uric Acid Levels

In order to compare the results of the serum uric acid estimations of our patients with those of the population survey carried out by Popert and Hewitt (1962), it was first necessary to establish that the two methods employed gave similar results. To do this, twenty sera from their survey were kindly sent for analysis in our laboratories, and our values were not significantly different from those obtained in Manchester.

In the 56 males and 43 females with polycythaemia vera, the serum uric acid levels were higher than in the general population (Fig. 1, opposite). As impaired renal function may cause a rise in serum uric acid, the thirteen patients (eight male and five female) whose blood urea was over 50 mg. per cent. were excluded. Even so, defining hyperuricaemia as a serum uric acid of above 6 mg./100 ml., 58 per cent. of the 48 male and 42 per cent. of the 38 female patients with polycythaemia vera fall into this category compared with 4.6 per cent. of the males and 1.26 per cent. of the females in the population survey.

When the patients considered to be in remission were reviewed, hyperuricaemia was found to persist in 45 per cent. of the twenty males and 31 per cent. of the 26 females (Fig. 2, opposite).

Serology

In three patients, one male and two female, all over the age of 65, the D.A.T. was positive at 1:16. They also had positive latex tests. None had clinical evidence of rheumatoid arthritis although two were thought to have degenerative joint disease. This incidence is in keeping with that found in population surveys (Kellgren and Lawrence, 1956). Three further male patients had a positive latex test and one of these had been thought to be suffering from rheumatoid arthritis.

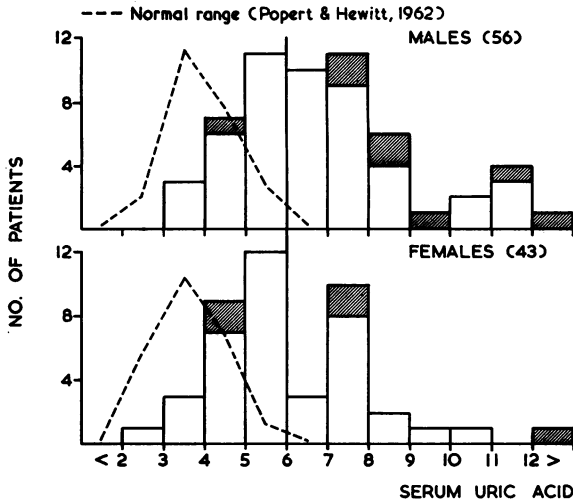


Fig. 1.—Serum acid levels in 99 patients with polycythaemia vera, compared with a population sample.

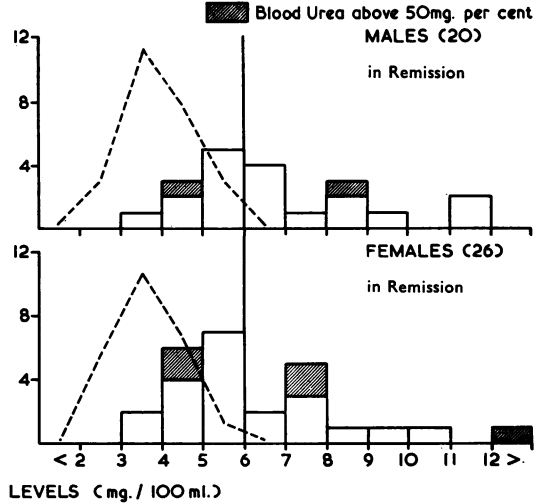


Fig. 2.—Serum uric acid levels in 46 patients in whom polycythaemia vera was in remission, compared with a population sample.

Radiological Findings

For the purpose of reading the radiographs of the feet, controls matched for sex and age were kindly supplied from the population survey of Wensleydale by Dr. J. S. Lawrence. The identity of the films was masked and after mixing, they were read for degenerative joint disease, cysts, erosions, rheumatoid arthritis, and gout at each of the following sites: interphalangeal joint of the great toe, first metatarsophalangeal joint, lateral metatarsophalangeal joints, and tarsus. The observed changes were graded 0 to 4 at each site.

Significant changes consistent with gout (Grade 2 to 4), were noted in the terminal interphalangeal joint on three occasions and on nine occasions in the first metatarsophalangeal joint (Fig. 3), compared with only one in the control group. In one patient the changes were confined to the terminal interphalangeal joint but the other two also showed metatarsophalangeal involvement. The overall incidence of degenerative changes in the first metatarsophalangeal joint was similar in the two groups, but the incidence of small cysts in the bones of the first metatarsophalangeal joint was greater in the polycythaemia patients (Table III, overleaf).

Correlation of Data

The serum uric acid of the fourteen patients with clinical gout, three of whom had a raised blood urea, ranged from 6.9 to 17.2 mg. per cent. (mean 9.3) compared with a range of 2.8 to 11.8 mg. per cent. (mean 6.2) in those with no history of gout: ten of this latter group had a raised blood urea. Changes consistent with gout were seen in the radiographs of

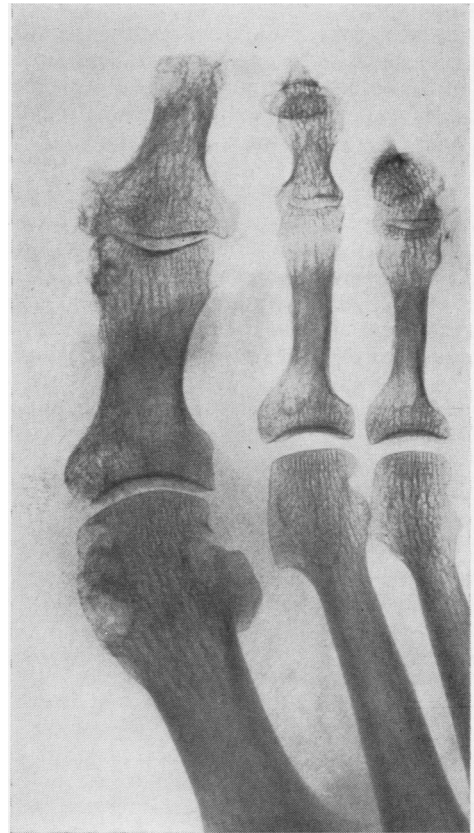


Fig. 3.—Cystic changes in the first metatarsophalangeal joint and interphalangeal joint of the great toe in a man aged 68 who had had polycythaemia vera for 8 years and gout for 4 years.

TABLE III

SIGNIFICANT RADIOLOGICAL FINDINGS IN THE FEET OF 94 PATIENTS WITH POLYCYTHAEMIA VERA COMPARED WITH 94 CONTROLS

Joints	Degenerative Joint Disease		Cysts		Gout	
	Controls	Patients	Controls	Patients	Controls	Patients
First Terminal Interphalangeal	18	12	7	7	0	3
First Metatarsophalangeal	52	58	16	39	1	9
Lateral Metatarsophalangeal	13	8	8	5	0	0
Tarsus	18	12	3	9	0	0

the feet in eight of the fourteen patients in whom a clinical diagnosis of gout had been made, while doubtful changes (Grade 1) were present in a further three. These eight patients diagnosed on both clinical and radiological grounds as having gout had higher serum uric acid levels (range 7.3 to 17.2 mg. per cent., mean 10.8), but they include three in whom the blood urea was raised. There were two patients with cystic radiological changes consistent with gout, but they had no history of acute episodes and had both been diagnosed clinically as cases of degenerative joint disease; the serum uric acid levels were 5.3 and 7.8 mg. per cent. respectively.

Discussion

The incidence of inflammatory polyarthritis either past or present did not differ from that recorded in population surveys (Kellgren, Lawrence, and Aitken-Swan, 1953). Assessed primarily on clinical grounds but taking into account the radiographs of feet and other radiographs when available, the incidence of degenerative joint disease was also similar to that in the population. It is, however, appreciated that the incidence of degenerative joint disease is best deduced from radiological evidence (Kellgren and Lawrence, 1958). Gout was diagnosed clinically in 14 per cent. in this survey and this was very much greater than would be expected for a population of this age and sex distribution and is higher than that found in any other published series (Tinney and others, 1945; Videbaek, 1950; Lawrence and others, 1953). It has been suggested that the diagnosis of gout requires more than a history of typical acute attacks (Kellgren, 1962). However, in the present survey, it was felt desirable to use only the history, as hyperuricaemia could not be relied on to confirm the diagnosis, being present in 38 patients with no history suggestive of gout, while tophi were noted in only one patient. Even the history may be difficult to interpret as, in the patients reviewed here, the attacks of gout were often transitory and usually did not recur after

successful treatment of the blood condition. Moreover, the symptoms of acute arthritis can be confused with the burning sensation and paraesthesiae in the extremities commonly encountered in polycythaemia. It was therefore valuable to have observed radiological changes in the great toe consistent with gout as supportive evidence in eleven cases. The absence of a family history in all but one patient, and the frequency with which females were affected is consistent with the findings of Gutman and Yü (1962), and with those in cases of gout secondary to other blood dyscrasias, such as congenital spherocytosis (Owen and Roberts, 1937) and thalassaemia (Vacrinos, Papaspyrou, Dandis, and Gallis, 1962).

In both males and females, in the absence of uraemia, hyperuricaemia was common, occurring in 58 and 42 per cent. respectively compared with an expected incidence of 4.6 per cent. in males and 1.26 per cent. in females. This accords with the findings of Stroebel and Law (1956). To investigate this phenomenon further, 24-hour urate clearances were performed in 52 patients who were admitted to hospital during the survey period; 26 (50 per cent.) had a urate clearance of less than 5 ml. per min., and when these were compared to the 26 whom the urate clearance was more than 5 ml. per minute, it was found that the mean serum uric acid level was higher, and the total urate excretion lower in those with impaired clearance and that it was only in this group that clinical gout had occurred. The impairment of renal function was reflected in the raised blood urea (above 50 mg. per cent.), which was present in eight of these patients (Table IV, opposite). It is, however, of interest that nine of the 26 patients with urate clearances of more than 5 ml. per min. had a serum uric acid level above 6 mg. per cent. When this data was reviewed according to the level of serum uric acid and presence of clinical gout, the mean urate clearance was considerably higher in the patients with normal serum uric acid levels than in those with hyperuricaemia, and this difference was

TABLE IV
URATE CLEARANCE IN 52 PATIENTS WITH
POLYCYTHAEMIA VERA

Patients with Polycythaemia Vera	Clearance of Uric Acid (ml./min.)	
	< 5	> 5
No. in Group	26	26
Mean Age (yrs)	62	62
Uraemia	8	0
Mean Serum Uric Acid (mg. per cent.)	8.8	6.3
Mean 24-hour Urinary Uric Acid (mg.)	479	712
No. with Clinical and Radiological Gout	8	0

even more obvious in the patients with gout (Table V).

TABLE V
CORRELATION OF HYPERURICAEMIA AND GOUT
WITH URATE CLEARANCE IN 52 PATIENTS WITH
POLYCYTHAEMIA VERA

Patients with Polycythaemia Vera	Serum Urate (mg. per cent.)		Clinical Gout
	< 6	> 6	
Total No. of Patients	14	30	8
No. Active at Time of Investigation	8	23	7
Mean age (yrs)	60	63	57.5
Mean Serum Uric Acid (mg. per cent.)	5.2	7.9	10.0
Mean 24-hour Urinary Uric Acid (mg.)	600	601	450
Mean Urate Clearance (ml./hr)	9.1	5.3	3.3
No. with Raised Blood Urea ..	0	6	2

It is unlikely that the hyperuricaemia associated with polycythaemia vera can be ascribed to a primary renal disorder. It is, however, possible that prolonged hyperuricaemia or perhaps some of the vascular complications of polycythaemia vera can cause impaired renal function in some patients, and that this then leads to an impaired urate clearance and in some cases to a rise in blood urea. The hyperuricaemia is most likely to arise from the underlying blood dyscrasia with its increased turnover of cells. The association between the haematological features of these cases and the serum uric acid levels are to be reviewed in a separate paper. (Denman, Szur, and Ansell, in press.)

Summary

(1) 101 unselected patients with polycythaemia vera attending a radiotherapy department have been reviewed with regard to rheumatic complaints. A

clinical diagnosis of gout was made in fourteen patients (nine men and five women). This is a considerably greater incidence than would be expected and is higher than that reported in most previously published series. The occurrence of inflammatory polyarthritis and degenerative joint disease did not differ from that in the general population.

(2) Taking 6 mg. per cent. as the upper limit of normal for serum uric acid levels, and excluding the thirteen cases with a blood urea above 50 mg. per cent., hyperuricaemia was found in 58 per cent. of the males and 42 per cent. of the females compared with an expected incidence of 4.6 per cent. in males and 1.26 per cent. in females, assessed for a population of this age distribution.

We should like to thank Prof. J. V. Dacie, Prof. I. D. P. Wootton, and Prof. R. E. Steiner for allowing the blood counts, urea, and uric acid estimations, and radiographs to be performed in their departments, Dr. Francis Scott for the differential agglutination titre and latex estimations, Dr. J. S. Lawrence for the control x rays and Dr. J. Popert and Miss V. Hewitt for the control sera.

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DISCUSSION

DR. C. F. HAWKINS (*Birmingham*): You mentioned that gout with tophi was very uncommon in polycythaemia. Is it any more common than in the general population?

DR. ANSELL: In fact we found only one. I am not quite certain of the exact incidence in gout, but perhaps Dr. Lawrence can tell us. It has already been suggested that tophi are rarely associated with gout in cases of thalassaemia; it has also been noted previously in the literature on gout and polycythaemia. I do not think that the answer can be *entirely* due to the fact that the patients do not live long enough.

PROF. E. G. L. BYWATERS (*Taplow*): Normally patients who come with gout to the clinic have a much higher proportion of tophi—in a population sample of gouty patients it would be very much lower.

DR. ALAN HILL (*Stoke Mandeville*): I should have put it at 10 per cent.

DR. G. D. KERSLEY (*Bath*): I think this is probably the answer. As Prof. Bywaters says, if you are going round looking for gout, rather than taking only the really severe cases which have to come to hospital, you will find a different percentage.

DR. C. R. CROFT (*Plymouth*): You mentioned that some of the patients had psoriasis. I wonder whether this was any more than a chance relationship.

DR. ANSELL: I am coming to believe that psoriasis is an extraordinarily common disease, which occurs coincidentally with very many disorders.

DR. G. D. KERSLEY (*Bath*): Again, you are looking and questioning for psoriasis, and probably quite a number of the cases you find may not be severe enough to attend a skin clinic.

PROF. E. G. L. BYWATERS (*Taplow*): There is a connexion between gout and psoriasis as there is between hyperuricaemia and psoriasis. People who have widespread psoriasis very often have high serum uric acid levels.

DR. ANSELL: But it so happens that all our five psoriatics had normal serum uric acid levels.

DR. J. S. LAWRENCE (*Manchester*): Has Dr. Ansell any idea why only some of the hyperuricaemics develop gout?

DR. ANSELL: I think that the serum uric acid level may well be related to urate clearance. In each of the cases diagnosed clinically as gout for which we have information, the urate clearance was markedly reduced, but those with hyperuricaemia alone showed no such marked reduction.

DR. M. R. JEFFREY (*Manchester*): Were any estimates of marrow function done? Radio-iron turnovers or the degree and rate of red cell formation might correlate a little better with the urate clearance.

DR. ANSELL: This was primarily a clinical survey carried out in the department of radiotherapy. The only things available to us were marrow films—taken from 52 of our patients at the same time as the serum uric acid estimations. We attempted to estimate the myeloid/erythroid ratios in these, but there was no close correlation with the serum uric acid. We did not do any turnover studies. We were only able to do the urate clearances because the patients had been admitted to hospital for some other treatment.

DR. ALAN HILL (*Stoke Mandeville*): Dr. Ansell was so careful to talk about degenerative joint disease instead of osteo-arthritis that I feel we might make a plea for dropping "inflammatory" as a redundant qualification of "polyarthritis".

Manifestations articulaires dans la maladie de Vaquez

RÉSUMÉ

(1) On a passé en revue 101 malades fréquentant un département de radiothérapie et atteints de maladie de Vaquez (polycythaemia vera) en recherche de manifestations rhumatismales. Un diagnostic clinique de goutte a été fait chez 14 malades (9 hommes et 5 femmes). On ne s'attendait pas à une si grande fréquence, supérieure à celle rapportée dans la plupart d'autres travaux publiés. La fréquence de la polyarthrite inflammatoire et de la maladie articulaire dégénérative ne se distinguait pas de celle dans la population générale.

(2) Si l'on prend 5 mg. pour cent comme limite supérieure normale de l'uricémie et l'on exclut treize cas d'urémie au dessus de 50 mg. pour cent, on trouve que 49 pour cent des hommes et 34 pour cent des femmes dans cette série avaient de l'hyperuricémie. Dans la population générale, d'âges similaires, la fréquence d'hyperuricémie est de 4,6 pour cent pour les hommes et 1,26 pour cent pour les femmes.

Manifestaciones articulares de la policitemia vera

SUMARIO

(1) Se investigaron 101 enfermos con policitemia vera que frecuentaron un departamento de radioterapia respecto a manifestaciones reumatoides. Se hizo un diagnóstico clínico de gota en 14 enfermos (9 hombres y 5 mujeres). Este incidencia fué considerablemente mayor a la anticipada y superior a la relatada en la mayoría de los trabajos publicados. La frecuencia de la poliartrosis inflamatoria y de la enfermedad articular degenerativa no difiere de la en la población general.

(2) A tomar el 5 mg. por ciento como límite normal superior de uricemia y con excluir trece casos de uremia de más de 50 mg. por ciento, se halla un 49 por ciento de los hombres y un 34 por ciento de las mujeres con hiperuricemia. En la población general, de edades similares, la frecuencia de hiperuricemia es de 4,6 por ciento en hombres y de 1,26 por ciento en mujeres.