

Serum uric acid in England and Scotland

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SUMMARY Serum uric acid (SUA) was measured in 512 men and 254 women from two English regions and in 337 men from one Scottish region. Mean SUA levels were the same in the men (5.5 mg/100 ml) and similar in the women (3.9 and 4.1 mg/100 ml). The apparent rarity of gout in Scotsmen cannot be explained by regional differences in SUA levels or in the prevalence of hyperuricaemia (defined as SUA of 7.0 mg/100 ml or over) which was present in 6.6% of the English men and 8% of the Scots. SUA was positively correlated with weight and serum urea, and with age in women, but no variation was found with social class. Body weight was the most important predictor of SUA in both men and women and superior to measurements involving correction for height, such as ponderal index and calculated lean body mass.

'In Scotland gout is much less frequently met with than in England . . . and when it does occur it is generally in the upper classes of society and in larger cities, where wines and ales have been largely substituted for whisky. . . . Sir Robert Christison bears similar testimony, for he informed me that he had met with only two cases of gout in the (Edinburgh) infirmary, although physician to it for 30 years, and both subjects were fat and overfed English butlers'.

A. B. Garrod in *Gout and Rheumatic Gout*, 3rd ed. 1876

The prevalences of gout and of hyperuricaemia are known to vary considerably between population groups in different parts of the world (Healey and Hall, 1970). One hundred years ago A. B. Garrod wrote that gout was far less common in Scotland than in England, a view which continues to be held, though actual data on this are lacking. In the absence of recent hypouricaemic therapy, hyperuricaemia is a prerequisite for the diagnosis of gout; it was therefore decided to compare serum uric acid (SUA) levels between adults in England and Scotland. At the same time the opportunity was taken to investigate other factors which are possibly related to SUA levels, such as physique, blood urea, and social class.

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Methods

A total of 1103 subjects took part in the survey, comprising 341 male and 52 female employees of the Atomic Energy Research Establishment, Winfrith, Dorset, England; 171 male and 202 female blood donors attending the Regional Blood Transfusion Centre, Birmingham, England; and 337 male employees of three light industry establishments in the Glasgow, Scotland area. (The number of female subjects from Glasgow (6) was too small for statistical analysis.) Subjects were interviewed at either blood donor sessions (Winfrith and Birmingham) or routine medical examinations (Glasgow) and asked to donate 10 ml blood. A record was made of each subject's sex, height, weight, and occupation, the last being coded into social class according to the Registrar General's Classification of Occupations (1970).

The serum was immediately separated from each blood sample and stored at -20°C. When all collections had been completed the sera were transported frozen to Charing Cross Hospital, London, for analysis. Mean storage time was 6.1 months. Serum urea and uric acid were measured colorimetrically on a Technicon autoanalyser (Technicon AA1-N30) in randomized batches of 30 sera for each run. The analysis sessions took place over three weekends and were carried out by the same senior technician and two assistants. Quality and drift control checks were carried out at frequent intervals throughout each session. As a final check three

samples from each run were carried over to the next run to exclude inter-batch variation. Daily means were calculated for each of the three regional groups and showed no significant variation.

Results

COMPARABILITY OF REGIONAL GROUPS

For the purpose of analysis the subjects were divided by sex and region of domicile. Mean ages, weights, and serum ureas for each group are given in Table 1.

The ages were similar apart from those of the Winfrith men which were significantly higher than any of the other four groups ($P < 0.01$). The Winfrith and Birmingham men were heavier than the Glasgow men ($P < 0.001$) and the Birmingham women were heavier than the Winfrith women ($P < 0.05$). The Birmingham men were taller than the Winfrith and Glasgow men ($P < 0.01$) and the Birmingham women were taller than the Winfrith women ($P < 0.01$). The Birmingham men had a lower mean serum urea than either of the other two males groups ($P < 0.001$). Combining the regions the men were of similar age (mean 37.2 years) to the women (mean 36.4 years) but heavier (mean 74.9 kg and 62.6 kg respectively; $P < 0.001$), taller (mean 175.3 cm and 162.9 cm respectively; $P < 0.001$), and with a higher blood urea (mean 30.8 and 26.4 mg/100 ml (5.1 and 4.4 mmol/l) respectively; $P < 0.001$).

FREQUENCY DISTRIBUTION OF SUA*

The SUA values were grouped into 0.5 mg/100 ml classes and plotted as a frequency distribution curve for each group (Fig. 1). The curves approximate a

* When the study was undertaken, uric acid levels were expressed in gravimetric (mg/100 ml) rather than in SI (mmol/l) units, and frequency distribution curves were drawn in classes of gravimetric units. These are therefore retained in this paper, giving the additional advantage of easy comparison with previous epidemiological studies. To convert mg/100 ml to mmol/l, the figure should be multiplied by 0.0595.

normal distribution, being slightly skewed towards the higher values, particularly in the women. No individual values were less than 1.3 mg/100 ml or greater than 8.9 mg/100 ml.

Uric acid levels for men were identical in the three regional groups, with a modal class of 5.5–5.9 mg/100 ml and a mean (\pm SD) of 5.5 ± 1.0 mg/100 ml. The modal class for the Winfrith women was 4.0–4.4 mg/100 ml and for the Birmingham women 3.5–3.9 mg/100 ml, the mean (\pm SD) being 4.1 ± 0.8 and 3.9 ± 0.8 mg/100 ml respectively. Combining the two female groups the modal class was 3.5–3.9 mg/100 ml and the mean 3.9 mg/100 ml.

AGE AND SUA

The mean SUA values for each 5-year age class, separated by sex, are shown in Fig. 2. The regional groups have been combined as the individual group plots closely overlapped. For adult men there is no significant correlation between SUA and age. The slight terminal rise should be ignored as it represents only 4 subjects. In women, however, the levels fall slightly at age 30–34 and thereafter gradually rise, more sharply after age 45–49, to reach a new higher level around age 55–59. Overall there is a significantly positive correlation between the individual SUA values in women with age and there is a highly significant difference ($t = 4.176$, $P < 0.001$) between the mean SUA in those under 50 (mean 3.8 mg/100 ml) and those 50 and over (mean 4.3 mg/100 ml). Analysis of variance confirmed that the differences between the age-specific mean SUA levels were unlikely to be due simply to sampling variations ($F = 2.756$; degrees of freedom = 9:244; $P < 0.01$).

Although there was considerable overlap between the individual male and female SUA values at most age groups, the mean values were all significantly different at the 1% level or less, using the t test.

WEIGHT AND SUA

The mean SUA levels for each 10-kg weight class are shown in Fig. 3. The regional groups are combined as there were no significant differences in SUA

Table 1 Number of subjects from each region with mean age, weight, height, and blood urea

	Men			Women	
	Winfrith	Birmingham	Glasgow	Winfrith	Birmingham
No. of subjects	341	171	337	52	202
Mean age (years)	41 ± 12	35 ± 12	35 ± 12	35 ± 13	37 ± 13
Mean weight (kg)	75.9 ± 9.5	77.5 ± 10.9	72.7 ± 10.3	59.9 ± 6.5	63.2 ± 9.6
Mean height (cm)	175.3 ± 6.5	177.3 ± 6.7	174.4 ± 6.5	160.8 ± 6.5	163.4 ± 6.5
Mean serum urea (mg/100 ml) \pm SD	31.3 ± 6.7	28.7 ± 6.1	31.4 ± 6.9	25.9 ± 5.8	26.5 ± 6.2

Conversion: Traditional units to SI—Urea: 1 mg/100 ml \approx 0.166 mmol/l.

levels for each weight class. There is a trend for SUA to rise with weight and for individual values the correlation is significant at the 1% level. Correlations were also drawn with Ponderal Index (PI), that is $Ht/(3\sqrt{Wt})$, and Lean Body Mass (LBM), calculated according to the formula of Hume and Weyers

(1971), and the results are shown in Table 2.

There was a significantly negative correlation with PI and a positive correlation with LBM but the correlation was no closer than that with weight. There was no correlation with height taken as a variable in its own right, in either sex.

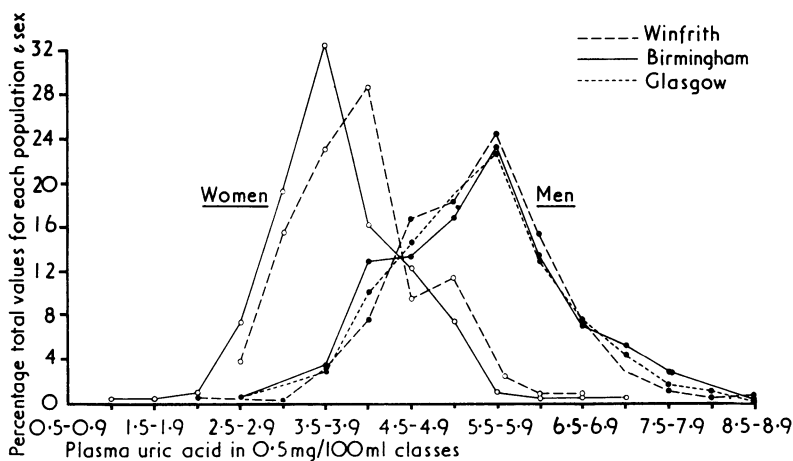


Fig. 1 Frequency distribution of serum uric acid levels for men and women.

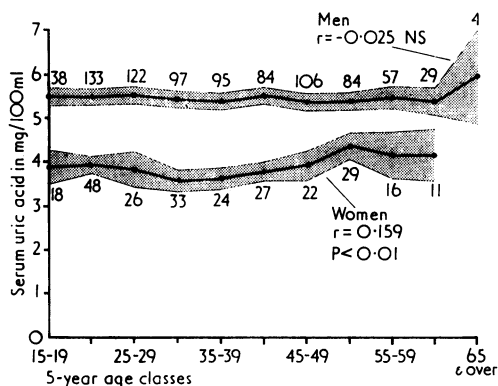


Fig. 2 Mean serum uric acid by 5-year age class. Numerals indicate number of subjects in each age class and stippled area represents 2 standard errors on either side of mean.

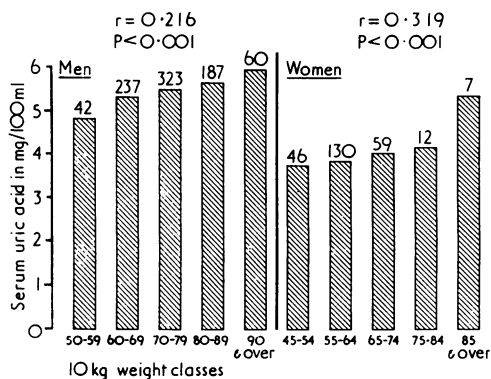


Fig. 3 Mean serum uric acid by 10-kg weight class. Numerals indicate number of subjects in each weight class.

Table 2 Correlation coefficients for serum uric acid (SUA) with height, weight, ponderal index (PI), and lean body mass

	Height	Weight	PI	LBM
Men	$r = 0.55, P > 0.1$	$r = 0.216, P < 0.001$	$r = -0.183, P < 0.001$	$r = 0.190, P < 0.001$
Women	$r = -0.027, P > 0.1$	$r = 0.319, P < 0.001$	$r = -0.299, P < 0.001$	$r = 0.146, P < 0.01$

SERUM UREA AND SUA

The mean SUA values for each 10 mg/100 ml class in blood urea are shown in Fig. 4 for the combined men and combined women. There were again no significant differences between the regional groups in SUA levels at each urea class. There is a trend for SUA to rise with increasing serum urea; this takes place even within the generally accepted range for normal urea values. For individual values the correlation is significant at the 1% level in men and 5% level in women.

HYPERURICAEMIA

Individual SUA values of 7 mg/100 ml or over were found in 19 Winfrith men (5.6%), 15 Birmingham men (8.8%), and 27 Glasgow men (8%), resulting in an overall prevalence of hyperuricaemia, defined in this way, of 7.2%. The regional differences were not significant using the χ^2 test with Yates's correction. Only one woman (0.4%) from Birmingham was hyperuricaemic.

Comparisons between the 788 normouricaemic and 61 hyperuricaemic men are shown in Table 3. The two groups were of similar age and PI but the

hyperuricaemic men were significantly heavier with a greater LBM and higher blood urea levels than the normouricaemic individuals.

MULTIPLE REGRESSION

A stepwise regression analysis was carried out to determine the relative contributions of each of the independent variables, shown previously to be significantly correlated, as predictors of SUA. The results are given in Table 4.

Sex was by far the most important predictor of SUA, accounting for 33% of the total variation (percentage variation accounted for = $R^2 \times 100$), the other variables adding only another 6%, although with the exception of PI their contribution to the SUA of the combined sexes were all statistically significant. Taking the sexes separately the variables considered accounted for 14% of the variation of SUA in the women but only for 8% in the men, with weight contributing 10% in the women and 5% in the men. PI and LBM were also more strongly correlated with SUA in the women than the men (Table 2) but only LBM in the women and PI in the men retained a significant contribution when entered

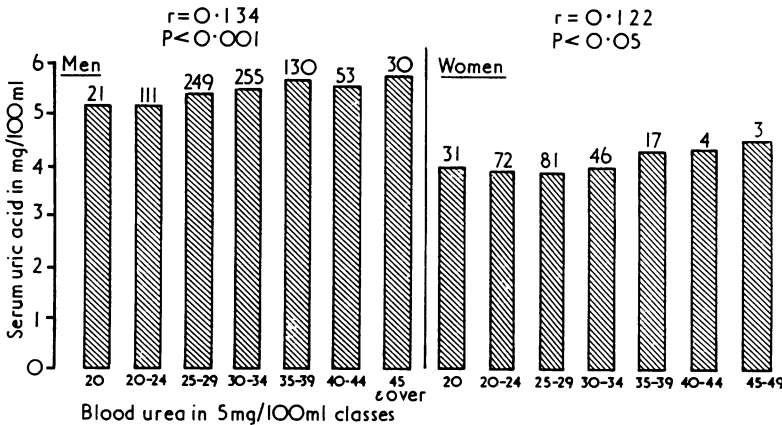


Fig. 4 Mean serum uric acid by 5 mg/100 ml serum urea class. Numerals indicate number of subjects in each urea class. Conversion: Traditional units to SI—Urea: 1 mg/100 ml \approx 0.166 mmol/l.

Table 3 Comparisons between normouricaemic and hyperuricaemic men

	Normouricaemic	Hyperuricaemic	t	P
Mean SUA \pm SD (mg/100 ml)	5.3 \pm 0.8	7.5 \pm 0.5	0.32	<0.001
Mean age \pm SD (years)	37.3 \pm 12.6	36.8 \pm 12.6	20.16	NS
Mean urea \pm SD (mg/100 ml)	30.7 \pm 6.6	33.0 \pm 7.2	2.57	=0.01
Mean height \pm SD (cm)	175.3 \pm 6.6	176.4 \pm 7.0	1.31	NS
Mean weight \pm SD (kg)	74.6 \pm 10.1	78.5 \pm 12.6	2.86	<0.01
Mean PI \pm SD	12.6 \pm 0.5	12.5 \pm 0.6	1.64	NS
Mean LBM \pm SD	57.9 \pm 5.1	59.8 \pm 6.3	2.71	<0.01

Table 4 *Stepwise regression of SUA with physique, blood urea, and age*

Step	Men			Women			Both sexes		
	Variable added	R	R ²	Variable added	R	R ²	Variable added	R	R ²
1	Weight*	0.216	0.047	Weight*	0.319	0.102	Sex*	0.571	0.326
2	Urea*	0.254	0.064	LBM†	0.349	0.122	Weight*	0.603	0.363
3	Age*	0.272	0.074	Urea	0.359	0.129	Urea*	0.611	0.374
4	PI†	0.283	0.080	PI	0.366	0.134	LBM*	0.615	0.378
5	LBM	0.285	0.081	Age	0.371	0.137	Age*	0.618	0.382
6	—	—	—	—	—	—	PI	0.618	0.382

* $P < 0.01$. † $P < 0.05$.

into the stepwise procedure; in neither case did this amount to more than 1% of the total variation of SUA. Interestingly, age, because of its association with previously entered variables, became insignificant as a predictor of SUA in women but attained a significant contribution in men. Similarly serum urea lost its significance in women but retained it in men.

SOCIAL CLASS AND SUA

The mean SUA values for each social class group are shown in Table 5. As there was under-representation of social class V this was combined with social class IV. Many of the Birmingham women gave their occupation as 'housewife' and were excluded from the analysis as this does not adequately represent their social class. Only in the Birmingham men was a consistent trend shown of SUA to rise with decreasing social class. As social class cannot be considered to be continuously distributed, the Birmingham figures were tested for significance by analysis of variance. No significant variation of SUA between the class groups was found ($F=1.125$; degrees of freedom 3:167).

Discussion

By separating the blood immediately, storing the sera in the frozen state, and analysing them in randomized batches over a limited number of sessions in one laboratory, the technical and inter-laboratory errors which can reduce the validity of population comparisons (Bywaters and Holloway,

1964) were minimized. The autoanalyser technique for measuring SUA is a colorimetric method and has been reported by most investigators to give readings 0.2 to 0.5 mg/100 ml higher than the more specific enzyme spectrophotometric method (Popert and Hewitt, 1962; O'Sullivan *et al.*, 1965; Evans *et al.*, 1969; Dodge and Mikkelsen, 1970). However, in our laboratory, comparison of the two methods gives a mean level of 0.3 mg/100 ml lower for the colorimetric method, as has been reported by other workers (Liddle *et al.*, 1959), and an overall correlation coefficient of 0.97. Storage should only improve the reliability of the method as it allows nonspecific chromogens to decay (Buchanan *et al.*, 1965).

Comparison of our findings with those of earlier surveys is difficult because of the above provisos and also because earlier nonautomated colorimetric procedures tend to give lower readings, of the order of 0.4 mg/100 ml, than the automated method (Finn *et al.*, 1966). Nevertheless, it is interesting to compare the present survey with the findings of other surveys in Caucasian adults of a similar age range to our subjects. Table 6 gives the mean levels and the percentage of those with an SUA of 7 mg/100 ml or over in surveys including over 100 subjects. Mean levels in the present study are higher than those in the only previous large scale United Kingdom survey (Popert and Hewitt, 1962), a finding unlikely to be accounted for entirely by methodological differences. They are also higher in men than those in a Finnish survey (Isomäki and Takkunen, 1969). They are similar to those of two surveys in the USA (Mikkelsen

Table 5 *Social class and serum uric acid*

	Mean SUA \pm SD for social class (numbers in parentheses)			
	I	II	III	IV & V
Winfrith men	5.5 \pm 1.0 (106)	5.5 \pm 0.9 (45)	5.5 \pm 0.9 (133)	5.3 \pm 0.9 (58)
Birmingham men	5.2 \pm 1.0 (20)	5.3 \pm 0.9 (25)	5.6 \pm 1.0 (111)	5.7 \pm 1.0 (15)
Glasgow men	5.4 \pm 0.5 (10)	5.5 \pm 1.0 (48)	5.5 \pm 1.0 (109)	5.5 \pm 1.0 (170)
Winfrith women	4.1 \pm 0.7 (6)	4.3 \pm 0.6 (2)	3.9 \pm 0.7 (34)	4.7 \pm 0.8 (10)
Birmingham women	3.9 \pm 1.0 (16)	3.8 \pm 1.0 (24)	4.0 \pm 0.7 (101)	3.7 \pm 0.6 (17)

Table 6 Mean SUA levels and percentage of hyperuricaemics in population surveys of over 100 subjects

Author & year	Location	No. of subjects	Age range (years)	Mean SUA (mg/100 ml)	Percentage of subjects with SUA 7.0 mg/100 ml or over	Method
Men						
Popert & Hewitt (1962)	Wensleydale, UK	411	15-74	4.45	2.4	Enzymatic
Acheson (1969)	Watford, UK	158	Adult	5.04		"
Mikkelsen <i>et al.</i> (1965)	Tecumseh, USA	2 142	15-74	5.25	9.38	"
Hall <i>et al.</i> (1967)	Framingham, USA	2 062	30-64	5.12	4.8	Colorimetric
Acheson & O'Brien (1966)	New Haven, USA	534	>21	6.37		"
Evans <i>et al.</i> (1969)	Carterton, NZ	202	>20	6.21		"
Jeremy & Towson (1971)	Sydney, Australia	500	19-59	6.28	23	"
Garrick <i>et al.</i> (1972)	Sydney, Australia	106	18-60	6.3	6 (>8.3 mg/100 ml)	"
Zalokar <i>et al.</i> (1972)	Paris, France	23 923	Adult	5.88	17.6	"
Isomäki & Takkunen (1969)	Saloinen, Finland	737	>16	5.0	5.2	"
Finn <i>et al.</i> (1966)	Liverpool, UK	267	Adult	5.41	8.2	"
Present study	UK	849	16-73	5.5	7.2	"
Women						
Popert & Hewitt (1962)	Wensleydale, UK	365	15-64	3.61	0.3	Enzymatic
Acheson (1969)	Watford, UK	163	Adult	4.20		"
Mikkelsen <i>et al.</i> (1965)	Tecumseh, USA	2 118	15-74	4.23	2.4	"
Hall <i>et al.</i> (1967)	Framingham, USA	2 489	30-64	4.01	0.4	"
Acheson & O'Brien (1966)	New Haven, USA	679	>21	4.72		Colorimetric
Evans <i>et al.</i> (1969)	Carterton, NZ	197	20-69	4.88		"
Garrick <i>et al.</i> (1972)	Sydney, Australia	110	18-60	4.6		"
Isomäki & Takkunen (1969)	Saloinen, Finland	1 048	18-60	4.0	1.2	"
Present study	UK	252	17-64	3.9	0.4	"

sen *et al.*, 1965; Hall *et al.*, 1967), a large French survey (Zalokar *et al.*, 1972), and a smaller British study (Finn *et al.*, 1966). They are considerably lower in both men and women than one other American survey (Acheson and O'Brien, 1966) and three Australasian surveys (Evans *et al.*, 1969; Jeremy and Towson, 1971; Garrick *et al.*, 1972).

Comparison of their findings with those of earlier Australian studies led Jeremy and Towson to suggest that there had been a true increase in SUA levels in the population over the previous 10 to 15 years and the same argument might apply when the present findings are compared with those of Popert and Hewitt. This would be in accord with the view that 'the associates of a high uric acid are the associates of plenty' (Acheson and Chan, 1969). However, sampling variation probably plays a large part in the differences between various surveys, particularly where the subjects are selected on the basis of employment or attendance at blood donor sessions.

For such reasons the subjects in this study may not have been completely representative of their regional population. However, when the regional groups were matched separately for age, physique, blood urea, and social class there were no significant differences in SUA levels between the groups (other than between the Winfrith and Birmingham women of social class IV/V). Indeed, the striking finding from this survey was the identical mean SUA level of the three male groups, and the closely similar levels in the two female groups.

The apparent rarity of gout in Scotland is unlikely therefore to be explained by regional differences in

SUA values. The prevalence of hyperuricaemia was a little lower, though not significantly so, in the combined English male groups (6.6%) than in the Scottish group (8.0%). It may be that Scotsmen are protected from the manifestations of gout in some other way; or, as we suspect, gout may have been uncommon in Scotland in the past but is less so today.

In certain populations and ethnic groups gout is said to be on the increase (Shichikawa, 1968; Talbott, 1976) and it might be expected that this would be mirrored in an increased prevalence of hyperuricaemia. Our findings cannot be taken to support this concept as far as the UK as a whole is concerned since, although the prevalence of hyperuricaemia in the men (Table 6) was higher than in one previous survey (Popert and Hewitt, 1962), it was very close to that in the other English group (Finn *et al.*, 1966). Selection factors may explain, at least in part, national and international differences, though much higher prevalence rates for hyperuricaemia were found in the French and one Australian study (Zalokar *et al.*, 1972; Jeremy and Towson, 1971). Similar considerations apply to the women although here there appeared to be closer agreement.

As expected, higher mean SUA levels were found in men than in women. The slight decrease in mean levels in women between the 3rd and 4th age decades is similar to that in other surveys and cannot be explained in terms of variations in obesity (Popert and Hewitt, 1962; Mikkelsen *et al.*, 1965; Evans *et al.*, 1969). The rise around the menopause has been

attributed to hormonal influences (Mikkelsen *et al.*, 1965), though a recent study carefully matching pre- and postmenopausal women of the same age (menopause defined as no menstruation during the previous 6 months) disclosed no difference between the two groups (Bengtsson and Tibblin, 1974). This definition of the menopause may not however exclude a falling-off of menstrual blood loss, and hence a rising haemoglobin, which is itself positively correlated with SUA (Acheson and O'Brien, 1966).

The known association of SUA with physique was also confirmed; it is of interest that there was a stronger correlation with body weight itself than with PI or LBM. Previous investigators have found a higher correlation with PI or relative body weight in men (Acheson and O'Brien, 1966; French *et al.*, 1967), though our findings are in agreement to the extent that both weight and PI are more strongly correlated with SUA in women than in men. Although women have more adipose tissue per unit body weight than men, they also have less lean body mass and it seems that total weight is a better predictor of SUA than either of the other two physique calculations in both sexes.

The association of SUA with serum urea levels, even within the normal range, is unexplained but has been noted before (Kennedy *et al.*, 1975), as has an association with serum creatinine (Decker *et al.*, 1968). Both renal and metabolic mechanisms could account for this; aging may contribute as highly significant correlations of serum urea with age were found in both men ($r=0.201$) and women ($r=0.355$).

The very large contribution of sex to the total variation of SUA when compared with the other variables implies that other sex-associated factors which have not been taken into account, possibly hormonal (Nicholls and Scott, 1972), contribute significantly to the sex differences in SUA levels. Age and serum urea are seen to be less important than body weight as predictors of SUA in women, but retain their significance in men. However, the contribution of all these variables, apart from sex, is very small in practical terms.

The absence of a significant relationship between SUA and social class is in keeping with earlier findings (Acheson, 1969), but true poverty was probably lacking in the groups studied by Acheson and ourselves.

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