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TITLE: "HYPERURICAEMIA IN ESSENTIAL HYPERTENSION
"AS SEEN AT KENYATTA NATIONAL HOSPITAL"

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A DISSERTATION SUBMITTED IN PART FULFILMENT FOR THE
DEGREE OF MASTER OF MEDICINE IN THE UNIVERSITY OF
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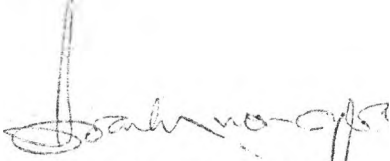


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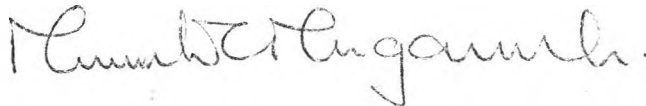
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I also feel very grateful to Mrs. Flora W. Nyaga for her meticulous secretarial work.

S U M M A R Y:

108 patients with essential hypertension have been followed up for 6 months ie Nov. 1979 - April 1980. 40 of these were newly diagnosed. The incidence of hyperuricaemia in the non-hypertensive population attending the Outpatient Department is ascertained and used as the control. It was found to be 4.8%. The incidence of hyperuricaemia in untreated patients with essential hypertension was found to be 27.5%. This incidence increased to 58.3% once anti-hypertensive therapy was commenced. Hyperuricaemia tended to occur in the severer grades of hypertension. Thiazide diuretics caused elevation of serum uric acid in those patients receiving it while guanethidine and alpha-methyldopa did not do so.

I N T R O D U C T I O N

An association between hyperuricaemia and hypertension was first described in 1957 (Duncan and Dixon, 1960) in a family attending the Hammersmith Hospital. The father and six children had hyperuricaemia while the mother and all the children had hypertension.

Subsequently hyperuricaemia with or without clinical gout has been widely documented in hypertensive populations (Camick et al, 1972). The high incidence of gouty persons who develop hypertension has been recognised for a long time and perhaps this is not surprising because of the known tendency of these persons to develop urate nephropathy (Talbot et al, 1960). Gouty persons have also been known to have systolic blood pressures averaging 12mmHg greater than the general population (Hall, 1965).

Hyperuricaemia has been shown to be common in patients with ischaemic heart disease (Kohn and Pozar 1959). A positive correlation has also been found between serum-cholesterol and serum uric acid in patients with ischaemic heart disease while Berkowitz, (1964) has shown an even closer relation between raised serum triglycerides and raised serum uric acid. Kramer et al (1958) found that 28% of patients with raised serum uric acid developed occlusive vascular disease of the limbs,

while Hansen (1964) found that of 41 patients with recent Cerebro-Vascular, accidents, none of whom had overt renal disease, 29% had a raised serum uric acid. The explanation for the close correlation between serum lipids especially the serum triglycerides and serum cholesterol and uric acid is not clear.

Hyperuricaemia is also common in patients with pre-eclamptic toxæmia (Chesley and Williams, (1945); consequently the level of serum uric acid has been used to judge the severity of the toxæmia process and may even be used to indicate the outcome of the pregnancy (Seitchik, 1953).

While following up a group of patients with a symptomatic hyperuricaemia (Assel et al (1971) found that these individuals had a wide range of biochemical and other findings that were statistically significantly different from those of a contrast group of Normouricaemic persons. Among these were; high levels of elevated systolic blood pressures. They had a high incidence of Rheumatoid factor and a high history of allergy to penicillin. He also found that both men and women maintained high levels of serum uric acid without developing gout, renal stones and azotemia. Later a significant number of these patients developed hypertension, heart disease and diabetes mellitus.

In separate studies Breckenbridge (1966) and Cannon et al (1970) found that approximately one quarter of untreated hypertensive patients without evidence of renal disease had hyperuricaemia.

Kinsey et al (1961) also found that 24% of patients with untreated hypertension had hyperuricaemia and that the treatment of hypertension quite substantially increased the incidence of hyperuricaemia in these patients. This later finding has also been found by Steele (1969).

It has come to be recognised that hyperuricaemia does occur in essential hypertensive patients without evidence of renal disease. Many clinicians treating these hypertensive patients with high serum uric acid values and who do not have any previous history of gout, have found it difficult in deciding to prescribe or stop prescribing a drug known to increase the level of serum uric acid for fear of precipitating attacks of gouty arthritis.

There are a number of studies in other countries done to ascertain the incidence of primary hyperuricaemia, but none has been done in Kenya. While studying serum uric acid values in rural Tanzanian Communities (Nhonoli and Kihama (1974) found the combined incidence of hyperuricaemia 3.5%. Grayzel and Liddle (1961) found the incidence of primary hyperuricaemia in the general health population to be 4.5% to 12%.

MATERIALS AND METHODS:

The study included a total of 108 patients. It covered both treated and untreated hypertensives whose systolic blood pressures were 160mmHg or higher and whose diastolic blood pressures were 95mmHg or higher.

At least two independent reading of the blood pressure were taken under basal conditions before the patient was admitted into the study. A mercury Syphgmanometer was used and the appearance of the first Korotkof sound taken to indicate systolic blood pressure while the change of the character of fourth korotkof sound indicated the diastolic blood pressure. Following this, a thorough physical examination and laboratory evaluation was carried out in each case to rule out as far as possible any cause of the elevated blood pressure.

Fourty of these patients were first seen by myself as referrals to the Medical Outpatient Clinic while the rest were seen at the Filter Clinic where they were first diagnosed and appropriate treatment commenced and subsequently seen by me during their two-monthly visits to the Medical outpatient Clinic. This is the group later refered to us "Untreated Hypertensives". The other sixty-eight patients were first seen at the Medical Outpatient Clinic or in the general medical wards having been admitted for control of blood pressure. This group had already been commenced on treatment before I saw them and they are subsequently referred to as "Treated Hypertensives".

All the patients in the study were reviewed after every two months for six months i.e November 1979 to April 1980 and at every visit, blood pressure was taken and blood specimens taken for serum creatinine, blood urea and serum uric acid-these are later referred to us 'relevant specimens'. Fundoscopy was done for most patients every visit, and the hypertensive retinal changes classified by means of Keith-Wagener Classification.

A separate group of one hundred and ninety eight patients who were attending KNH for minor illnesses i.e abdominal pains, minor respiratory infections, various forms of anxiety states etc had their blood pressures estimated under the same conditions as mentioned above. Those found to have normal blood pressure had blood specimens obtained for estimation of serum uric acid. Their age and sex was also recorded-and this is the group later referred to us "controls".

The thirty-two patients admitted to the wards for the control of blood pressure had besides the above investigations, twenty-four hour specimens of urine collected together with a blood sample for the estimation of creatinine clearance.

Nineteen patients in the "Untreated Hypertensive group were started on Hydroflumethazide 100 mgs daily, the rest had other drugs added to their therapy as their blood pressures required to be controlled urgently. These nineteen patients were followed for six months at two monthly intervals. In the "Treated Hypertensives" group, thirty two patients were started on alpha--methyl dopa 250mgs three times a day or a higher dose depending on the blood pressure and followed for four months at two-monthly intervals and lastly a further group of twenty three patients in the "Treated Hypertensives" group were started on Guanethidine 40mgs once daily or higher dosages depending on the value of the blood pressure and followed for four months at two-monthly intervals.

Sex, age were recorded for every patient in the study. The upper limits of normal serum uric acid were taken as 7 mgs per 100mls for males and 6mgs per 100mls for females.

At these levels it was hoped that those patients with; marginally elevated serum uric acid were excluded. The normal upper and lower limits as 40 and 16 mgs 100mls respectively.

All the blood specimens were analysed in the Clinical pathology Department of KNH by the use of Technicon SMA 11 system which is internationally standardised. The uric acid was measured by Modified Brown Method which is based on the reduction of phosphotungstate complex. Sodium tungstate is used as an alkalinising agent and hydroxylamine is added to intensify the colour. The absorbance of the analytical stream is measured at 660um.

The Technicon method for the measurement of serum creatinine is based on the reaction of picric acid with creatinine in the presence of an alkali. After dilution with sodium chloride and purification by dialysis it is alkalinised and the absorbance of the analytical stream is measured at 505um.

The determination of blood urea nitrogen is a modification of carbamido-diacetyl reaction. In a relatively weak acid solution diacetyl monoxime is hydrolysed to diacetyl which in turn reacts directly with urea and after colour intensification of the absorbance of the stream is measured at 570um.

The specimens for the Creatinine clearance were analysed in the same laboratory mentioned above but the calculation of clearance values was done by myself using the formula below.

$$C = \frac{UV}{P}$$

Where

C= Creatinine clearance in mls per minute

U= Concentration of Creatinine in the urine in
mgs per 100mls.

V= Volume of urine in mls per minute

P= Plasma concentration of creatinine in mgs
per 100mls.

The values of serum uric acid, serum creatinine
and blood urea were converted from SI_m MOLES/L
to SI mgs/dL so that results could be compared
to others done elsewhere.

RESULTS:1. AGE DISTRIBUTION:

Fig 1 is a histogram showing the age distribution of the 108 patients (females and males) in the study. Their ages ranged from 26 years to 69 years with a mean age of 39 years. 67% of the patients were of ages between 30 years and 50 years.

Controls

Fig 2 and 3 show the distribution of serum uric acid in the male and the female controls respectively. The distribution of serum uric acid is normal. There were 111 males whose mean age was 43.7 years while their serum uric acid was 4.7 ± 1.49 mgs % (mean \pm standard Deviation). Their serum uric acid values ranged from 2.3 mgs % to 7.7 mgs %.

There were 96 females whose mean age was 41.2 years while their serum uric acid was 4.0 ± 1.55 mgs % (mean \pm standard Deviation). The serum uric acid values ranged from 2.3 mgs % to 6.8 mgs %. The age for the male controls ranged from 20 years to 76 years while for female controls it was 24 years to 70 years.

The combined incidence of hyperuricaemia in the controls was 4.8 % which is higher than 3.5 % found by Nhomoli and Kihama (1974) while studying serum uric acid in Tanzania rural communities.

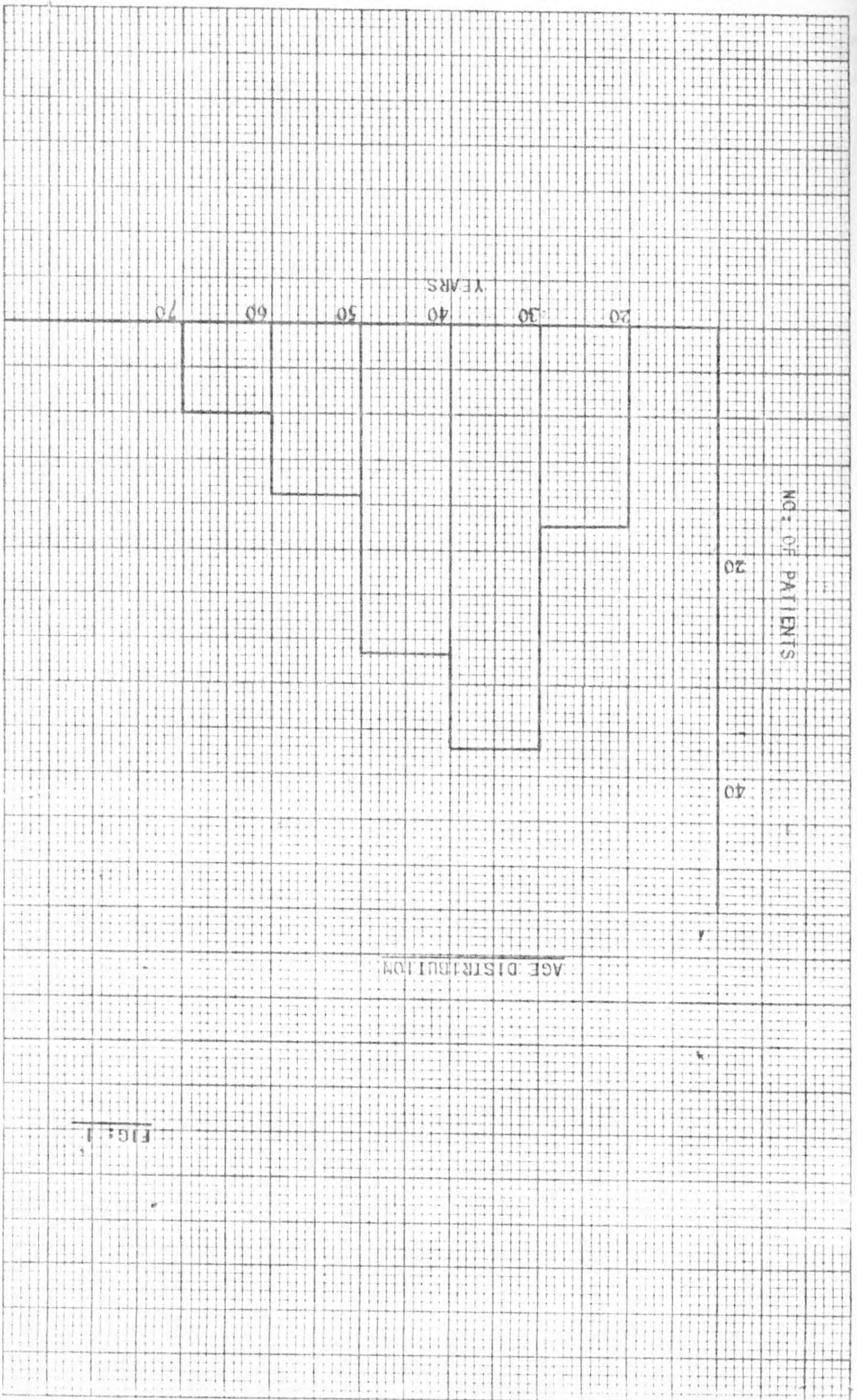


FIG: 1

FIG: 2

DISTRIBUTION OF SERUM URIC ACID IN
111 MALES ATTENDING K. N. H.

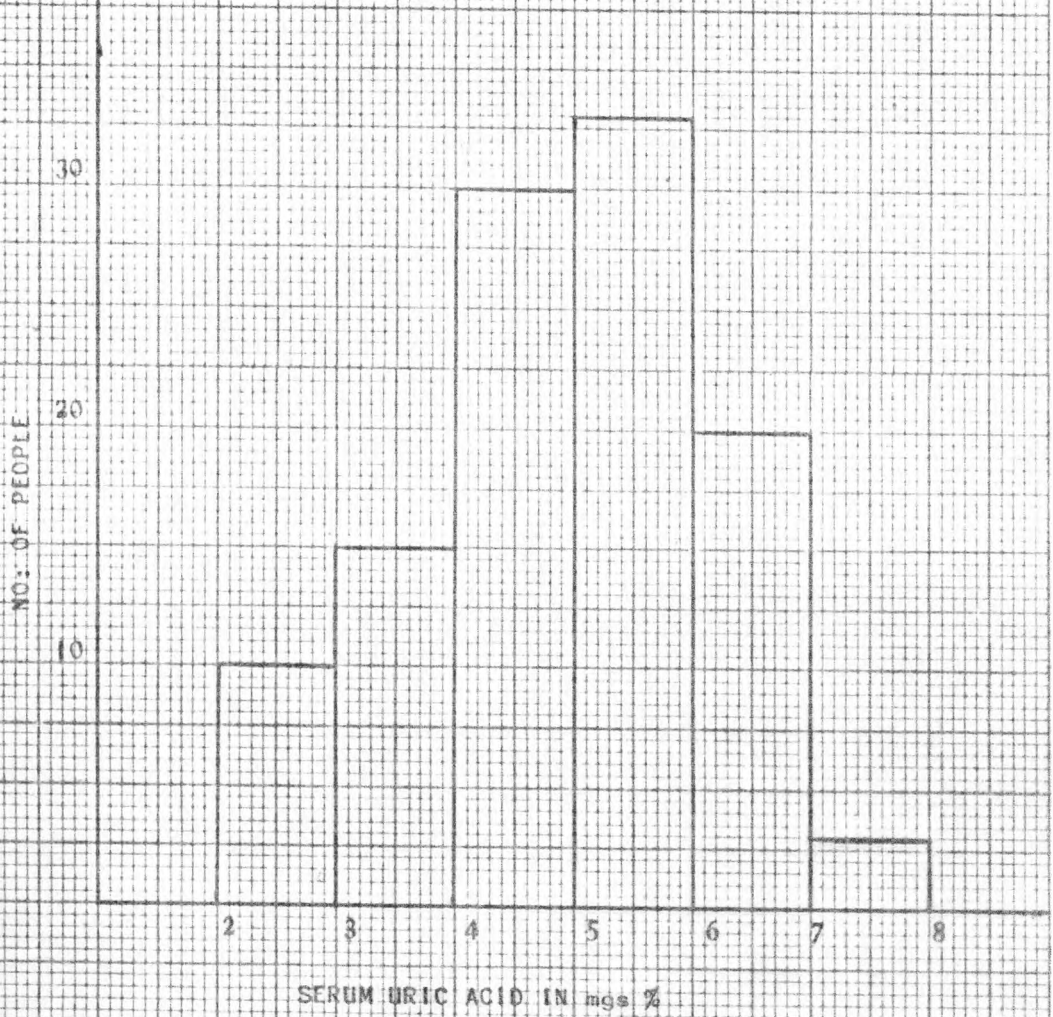
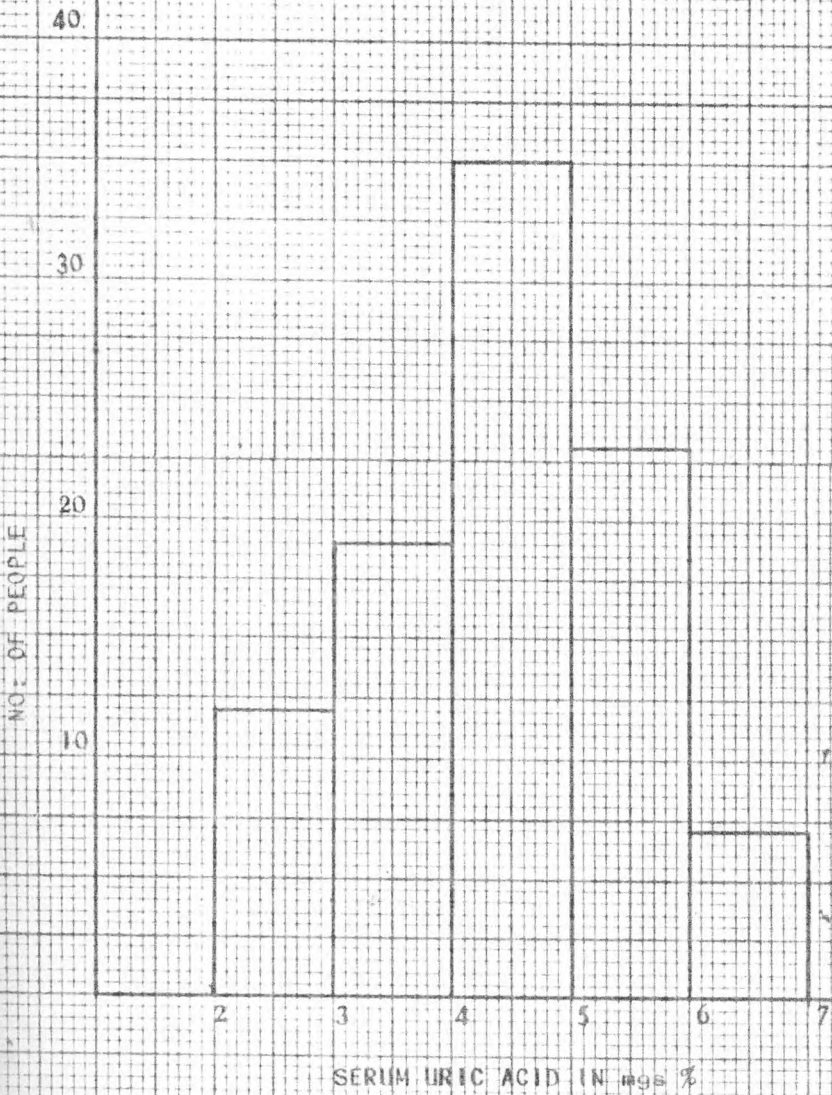


FIG: 3

DISTRIBUTION OF SERUM URIC ACID IN
96 FEMALES ATTENDING K. N. H.



2. INCIDENCE OF HYPERURICAEMIA

Table 1 shows the incidence of hyperuricaemia in the treated and untreated hypertensive patients. There was 58.3% incidence of hyperuricaemia in the treated group while in the untreated group it was 27.5% by the use of unpaired T -test of significance the difference between these two incidences was shown to be statistically significant ($P < 0.001$). By the use of the same test of significance mentioned above the difference between the incidence of hyperuricaemia in the study group and the control group was also to be highly statistically significant ($p < 0.001$).

TABLE I

HYPERURICEMIA IN TREATED AND UNTREATED
HYPERTENSIVE PATIENTS

SEX	TREATED HYPERTENSIVE PATIENTS		UNTREATED HYPERTENSIVE PATIENTS	
	NO.	NO. OF PATIENTS WITH RAISED S. U. A.	NO.	NO. OF PATIENTS WITH RAISED S. U. A.
MALE	58	35 (60.3%)	23	7 (30.4%)
FEMALE	50	28 (56%)	17	4 (23.5%)
TOTAL	108	63 (58.3%)	40	11 (27.5%)

Key

S.U.A. - SERUM URIC ACID

3. SERUM UREA IN TREATED AND UNTREATED HYPERTENSIVES.

Fig 5 shows the distribution of serum urea in 40 untreated hypertensive patients while Fig. 6 shows the distribution of serum urea in 108 treated hypertensive patients. Taking 40 mgs per 100 mls as the upper limit of normal blood urea, we find that only 2 out of 40 patients in the untreated group had elevated blood urea i.e 5% while only 8 out of 108 patients (7.4%) with treated hypertension had elevated blood urea. The differences were not significant.

The highest recorded blood urea was 47.5 mgs per 100mls, the same patient had serum uric acid of 7.2 mgs per 100 mls and a serum creatinine of 0.7 mgs per 100 mls.

FIG. 5

BLOOD UREA IN FORTY UNTREATED HYPERTENSIVES

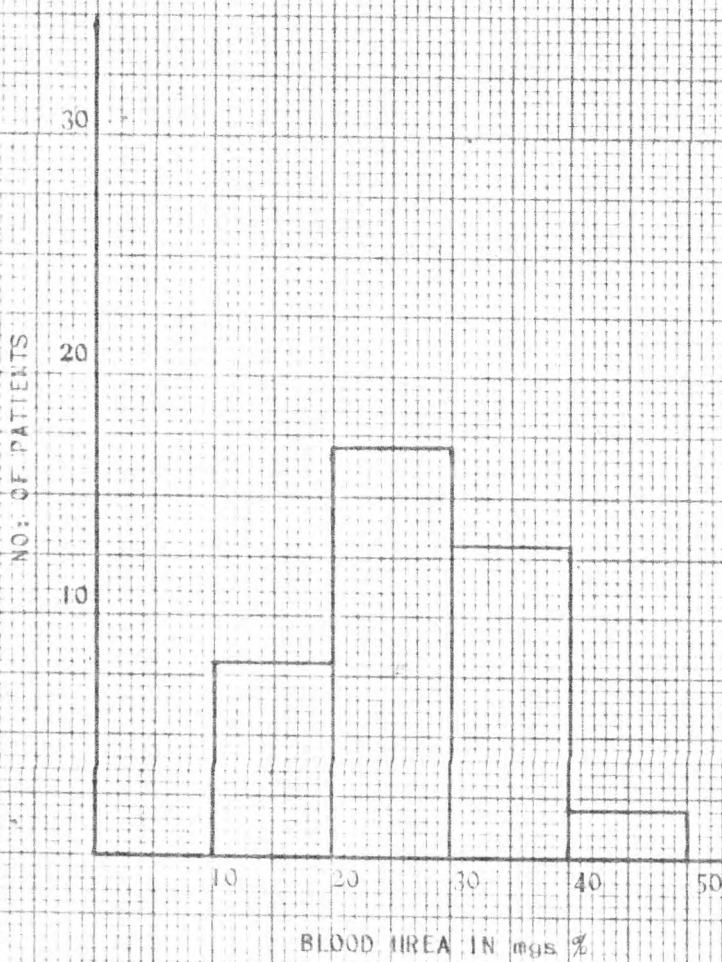
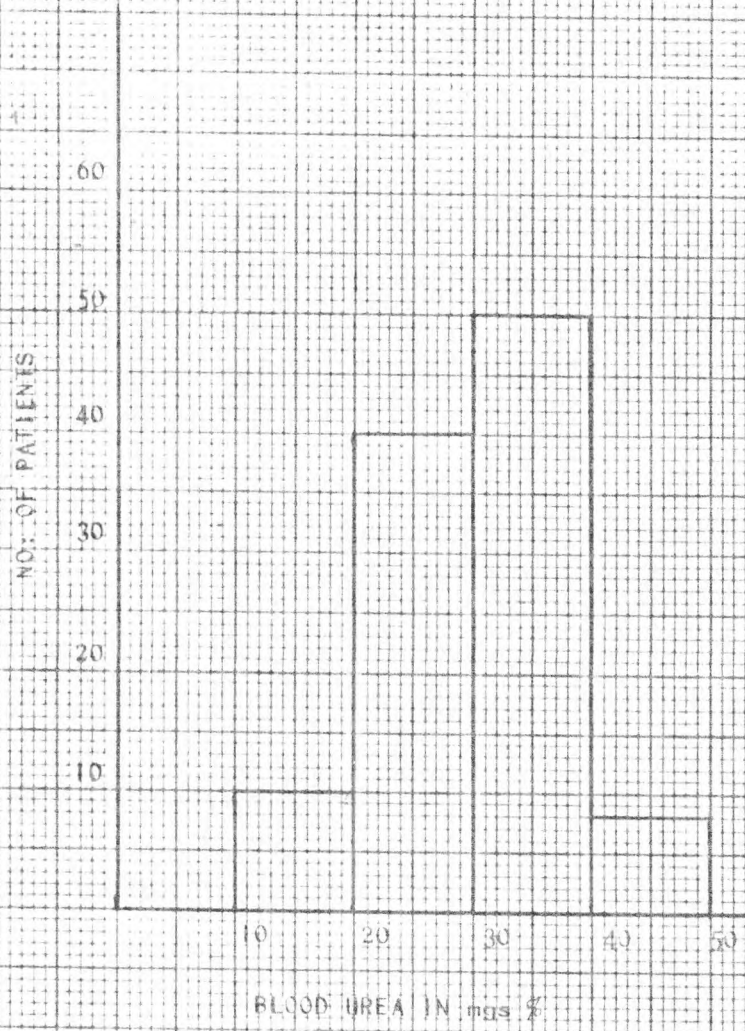


FIG. 6

BLOOD UREA IN 108 TREATED HYPERTENSIVE PATIENTS



4. SERUM URIC ACID AND BLOOD UREA IN
HYPERTENSIVE PATIENTS

Fig 7 shows that the distribution of serum uric acid and blood urea in 108 hypertensive patients by means of a scatter diagram. Absolutely no relationship is shown between these two parameters the (correlation coefficient $r=0$), which meant that the serum uric acid and blood urea are independent of each other in the patients.

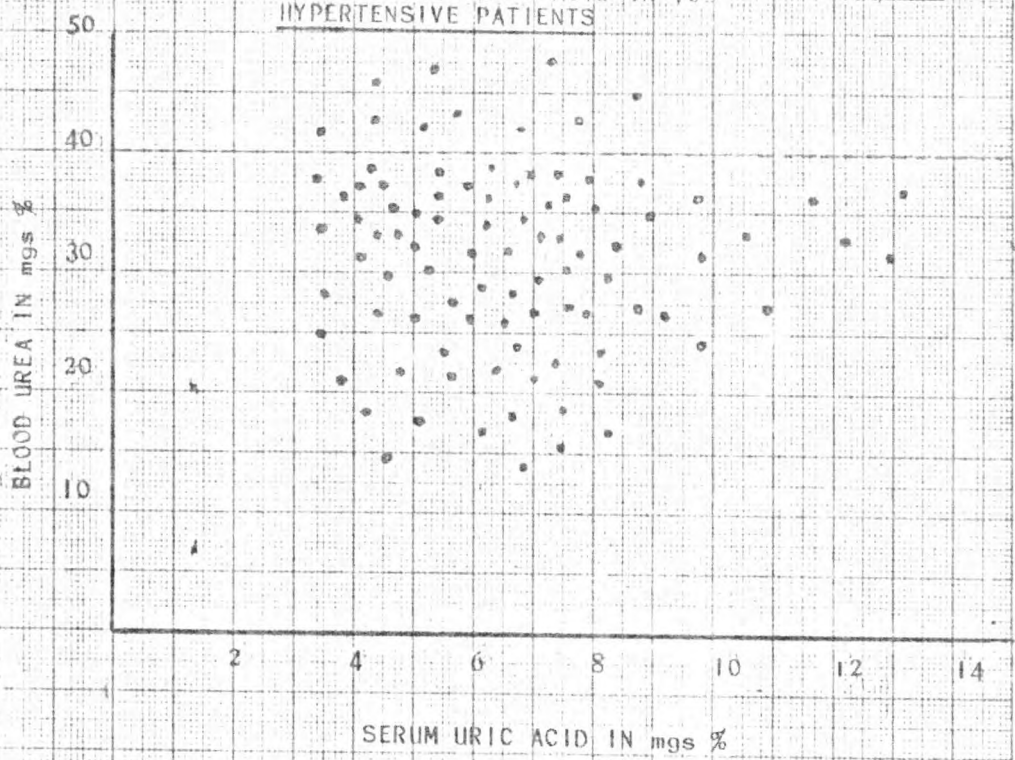
Fig 8 shows the distribution of serum creatinine and serum uric acid in 108 hypertensive patients. Again no relationship is demonstrated between (correlation coefficient $r=0$).

SERUM CREATININE IN TREATED HYPERTENSIVE PATIENTS.

Fig 9 shows the distribution of serum creatinine in 108 treated hypertensive patients. Taking 1 mg per 100 mls as the upper limit of normal only 7 out of 108 (6.5%) patients had elevated serum creatinine.

BLOOD UREA AND SERUM URIC ACID IN 108 HYPERTENSIVE PATIENTS

FIG: 7



SERUM CREATININE AND SERUM URIC ACID IN 108 HYPERTENSIVE PATIENTS

FIG: 8

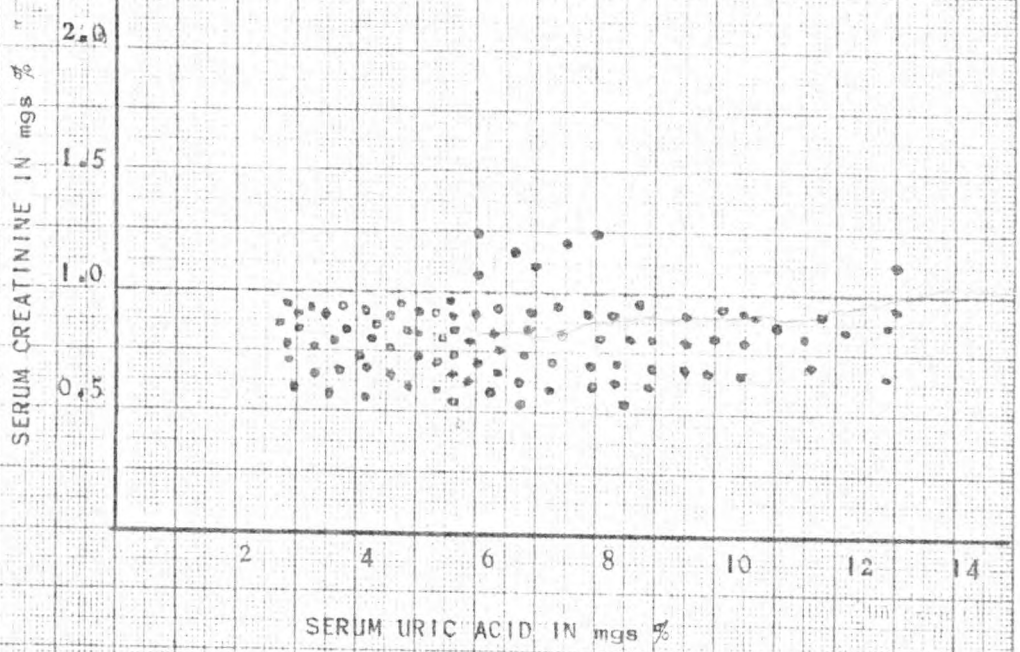
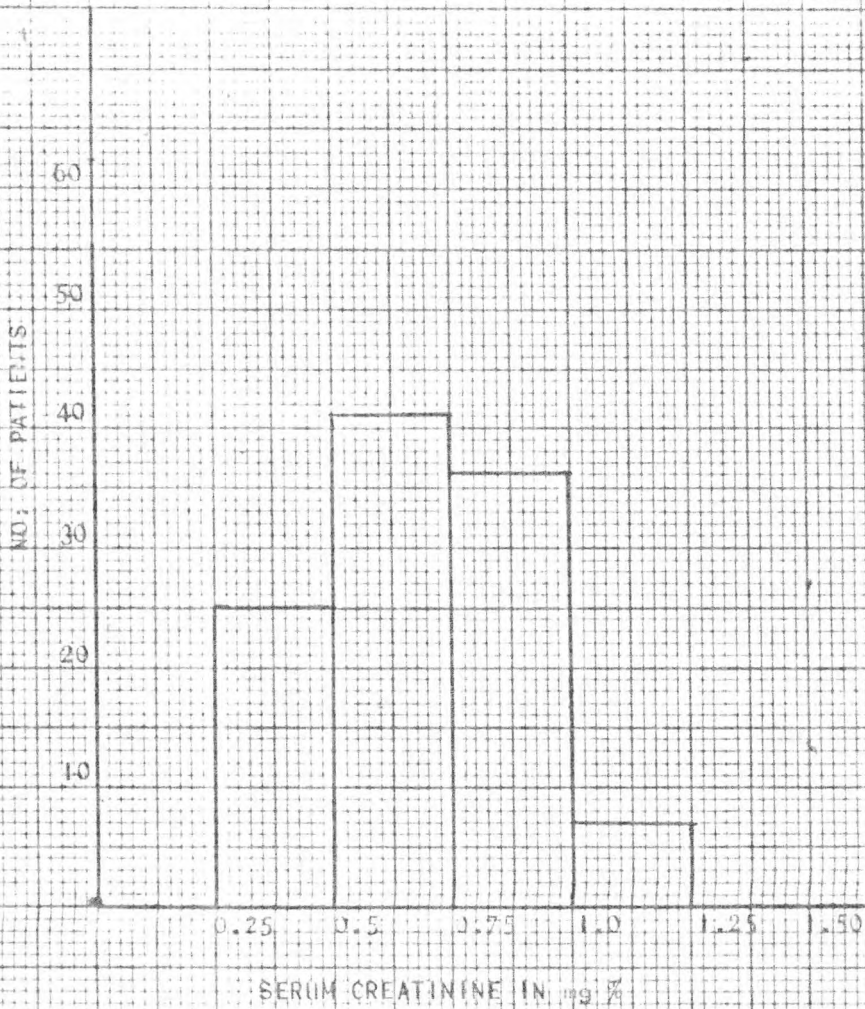


FIG: 9

SERUM CREATININE IN 108 HYPERTENSIVE PATIENTS



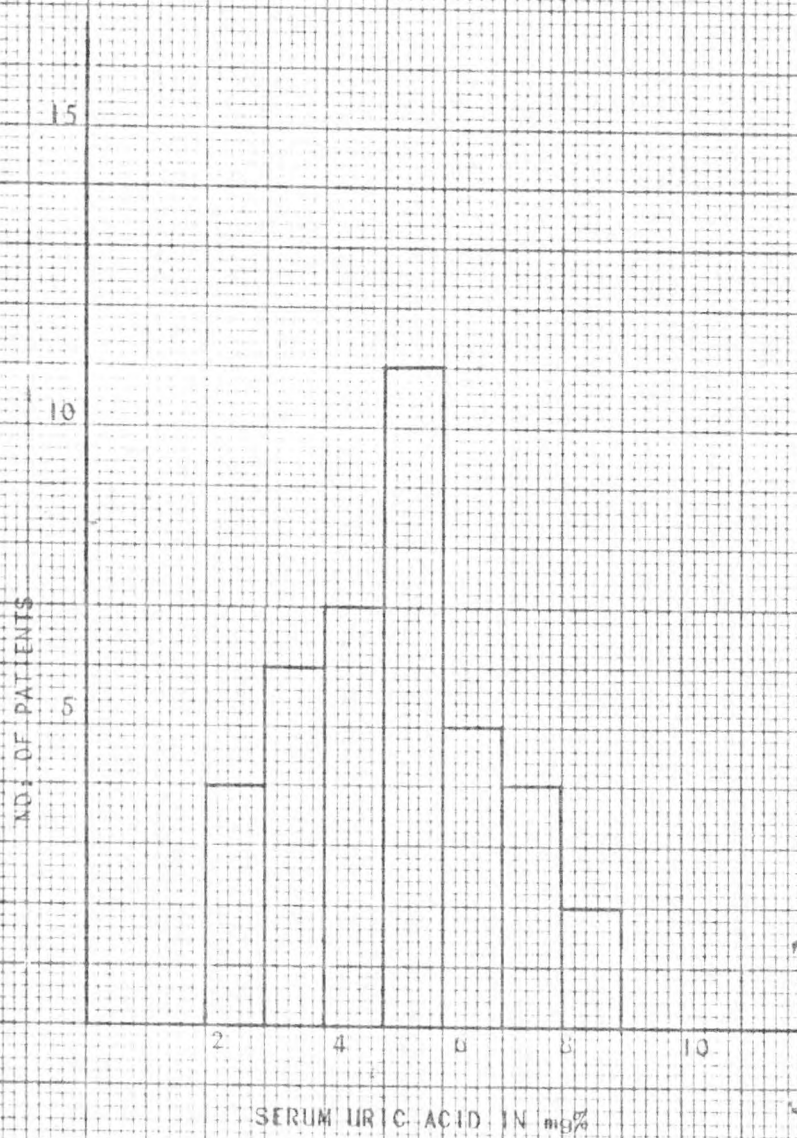
5. DISTRIBUTION OF SERUM URIC ACID

Fig. 10 shows the distribution of serum uric acid in 40 patients with untreated hypertension. Taking 6 mgs per 100 mls and 7 mgs per 100 mls as the upper limits of normal respectively, only 11 out of 40 patients (27.5%) had hyperuricaemia in this group of patients.

Fig. 11 shows the distribution of serum uric acid in 108 patients with treated hypertension. Again taking the upper limits of normal serum uric acid as shown above, 63 out of 108 (58.3%) had hyperuricaemia.

FIG. 10

SERUM URIC ACID IN 40 PATIENTS WITH UNTREATED HYPERTENSION



6. SEVERITY ON HYPERTENSION IN HYPERURICAEMIC AND NORMOURICAEMIC PATIENTS:

Fig. 12 (i) shows the distribution of severity of hypertension as graded by means of Keith-Wagener classification in 58 patients (39.6%) had grade 3 hypertensive retinopathy.

Fig. 12 (ii) shows the distribution of severity of hypertension by the use of the above grading system in 32 patients with normal serum uric acid and on treatment for hypertension. Only 5 out of 32 patients (18.6%) in this group had grade 3 hypertensive retinopathy. The unpaired T-test was used and the difference between these two figures was found to be statistically significant ($p < 0.001$).

Fig. 13 (i) shows the distribution severity of hypertension in 29 patients with normal serum uric acid who had not been commenced on treatment for hypertension. Only 6 out of 29 patients (20.7%) had grade hypertensive retinopathy in this group.

Fig. 13 (ii) shows the severity of hypertension in 11 patients with elevated serum uric acid who had not been commenced on treatment for hypertension. 5 out of 11 patients (45.4%) had grade 3 hypertensive retinopathy in this group. No papilloedema was seen in any of the patients.

FIG. 11

SERUM URIC ACID IN 108 PATIENTS WITH TREATED HYPERTENSION

NO: OF PATIENTS

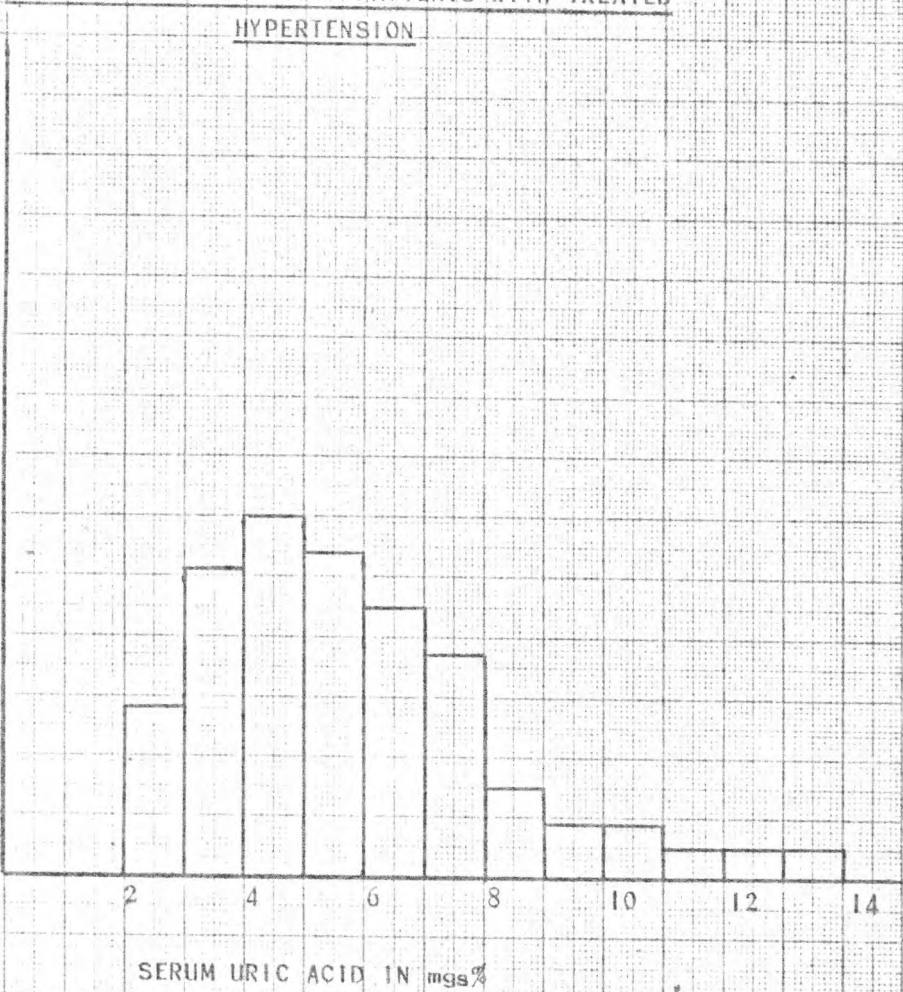


FIG: 12 (i)

SEVERITY OF HYPERTENSION IN 58 PATIENTS WITH ELEVATED SERUM URIC ACID

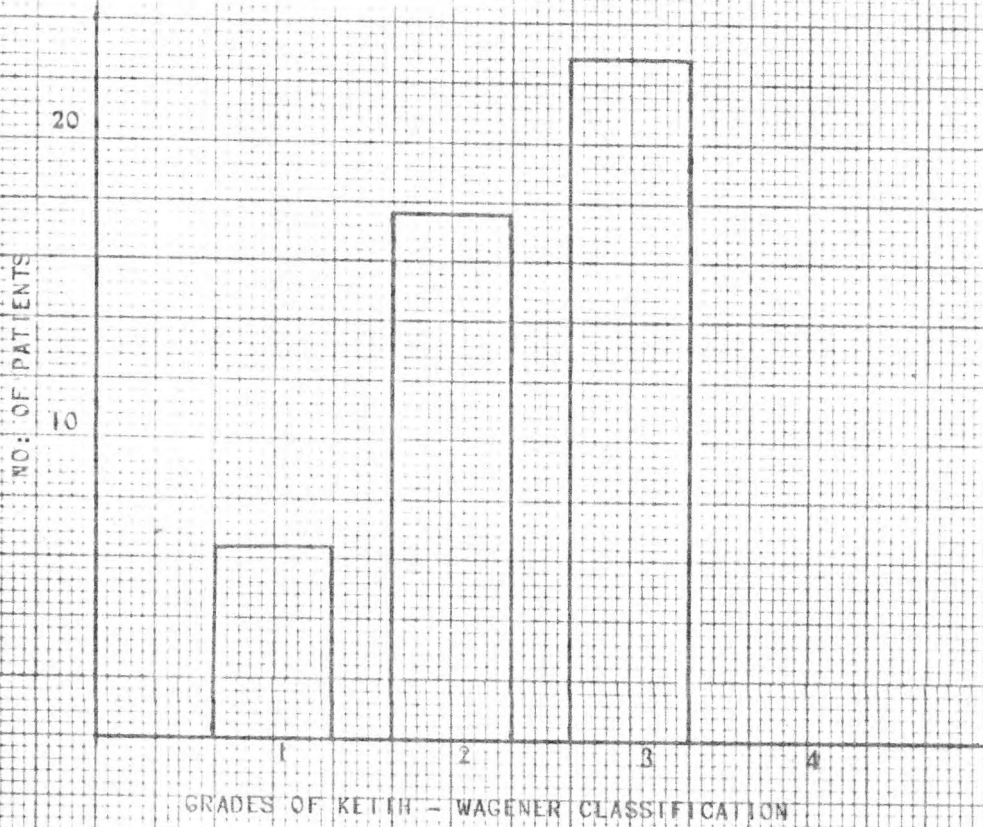


FIG: 12 (ii)

SEVERITY OF HYPERTENSION IN 32 PATIENTS WITH NORMAL SERUM URIC ACID

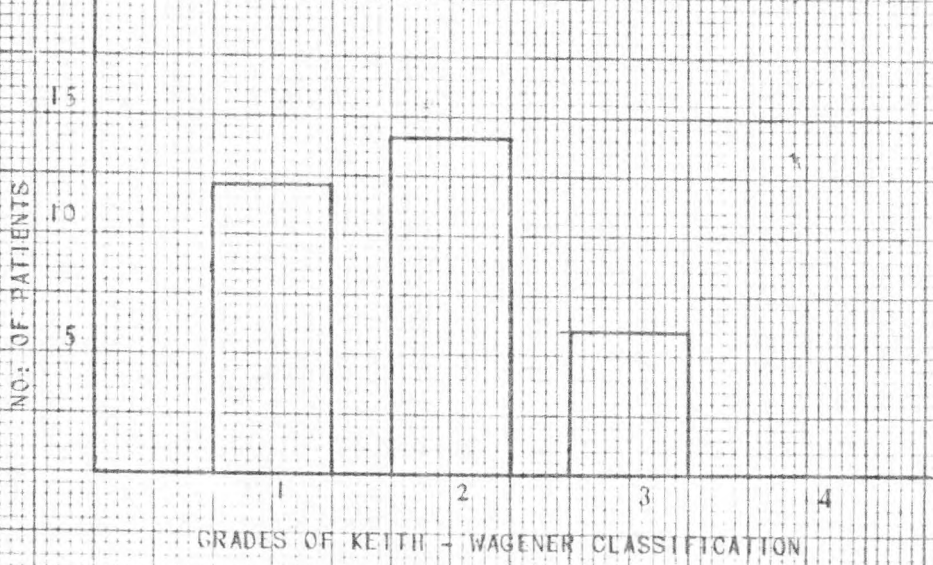


FIG: 13 (i)

SEVERITY OF HYPERTENSION IN 29 UNTREATED PATIENTS
WITH NORMAL SERUM URIC ACID

NO. OF PATIENTS

15
10
5

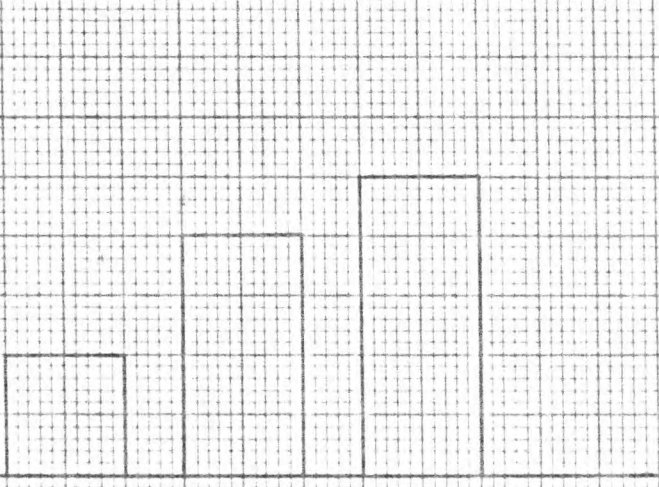
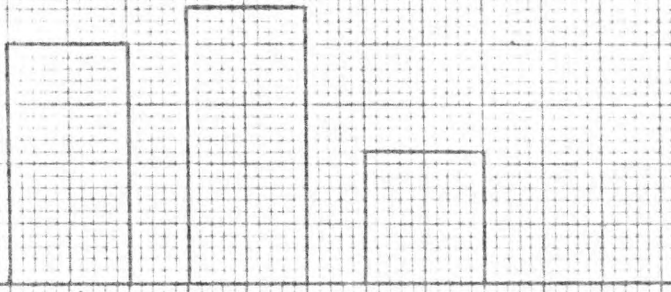
1 2 3 4
GRADES OF KEITH - WAGENER CLASSIFICATION

SEVERITY OF HYPERTENSION IN 11 UNTREATED PATIENTS
WITH ELEVATED SERUM URIC ACID

NO. OF PATIENTS

7
6
5
4
3
2
1

1 2 3 4
GRADES OF KEITH - WAGENER CLASSIFICATION



7. EFFECT OF HYPERTENSIVE THERAPY ON SERUM URIC ACID.

Fig 14 (i) shows the distribution of serum uric acid in 19 patients who had received hydroflumethiazide for 6 months. The histogram shows the marked shift towards hyperuricaemia, taking into consideration that these patients were "untreated Hypertensives" before commencing the treatment.

Fig 14 (ii) shows the distribution of serum uric acid in 30 patients who had received alphamethyldopa alone for 4 months. The drug did not have any appreciable effect on the serum uric acid again taking into consideration that this group of patients had been receiving other forms of anti-hypertensive therapy before commencing on alphamethyldopa.

Fig 15 shows the distribution of serum uric acid in 23 patients who had received guanethidine for 4 months. The drug also had little effect on the serum uric acid again bearing in mind that these patients were on other forms of anti-hypertensive therapy before being commenced on guanethidine alone.

FIG: 14 (i)

SERUM URIC ACID IN 19 PATIENTS WHO HAD RECEIVED HYDROFLUMETHIAZIDE ALONE FOR 6 MONTHS

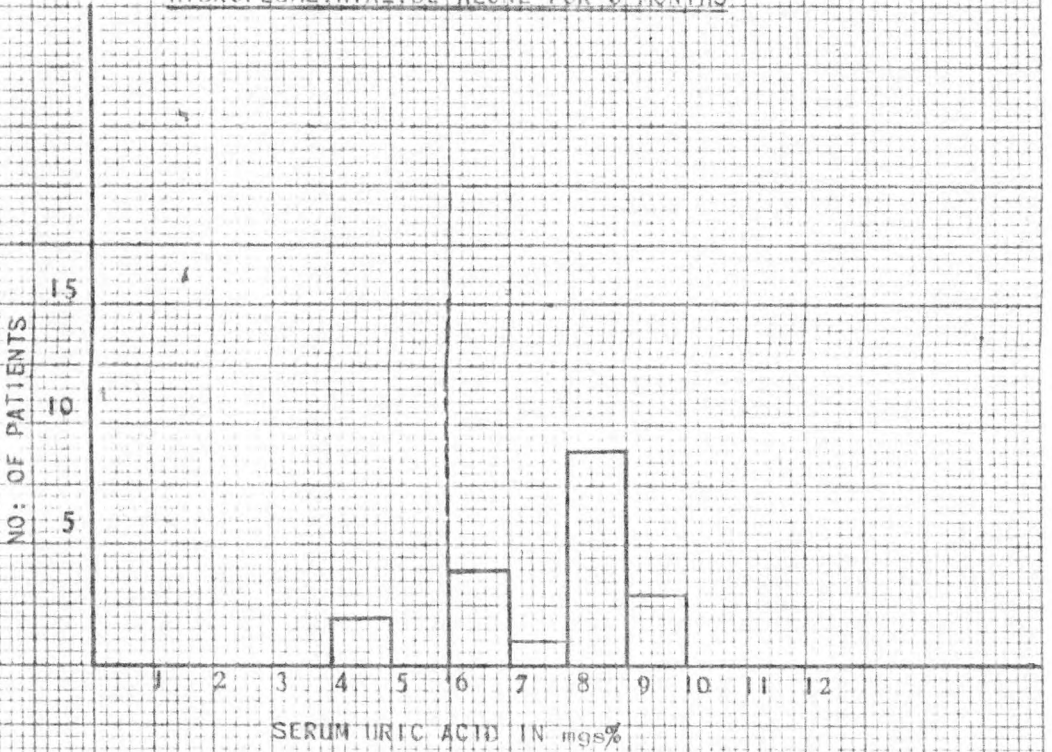


FIG: 14 (ii)

SERUM URIC ACID IN 30 PATIENTS WHO HAD RECEIVED ALPHA-METHYLDOPA ALONE FOR 6 MONTHS

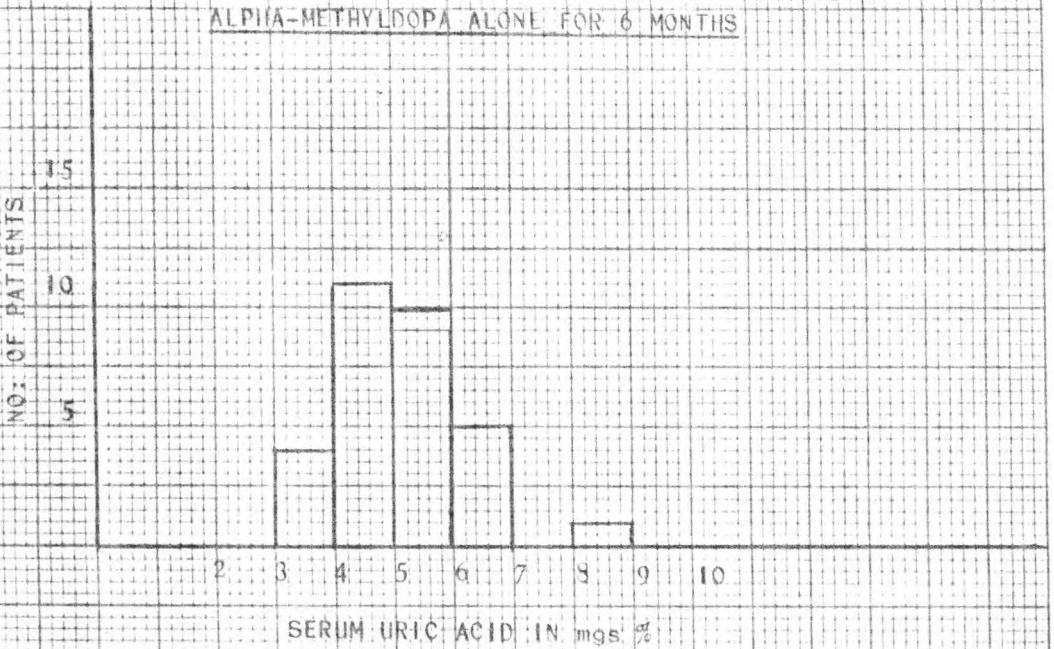
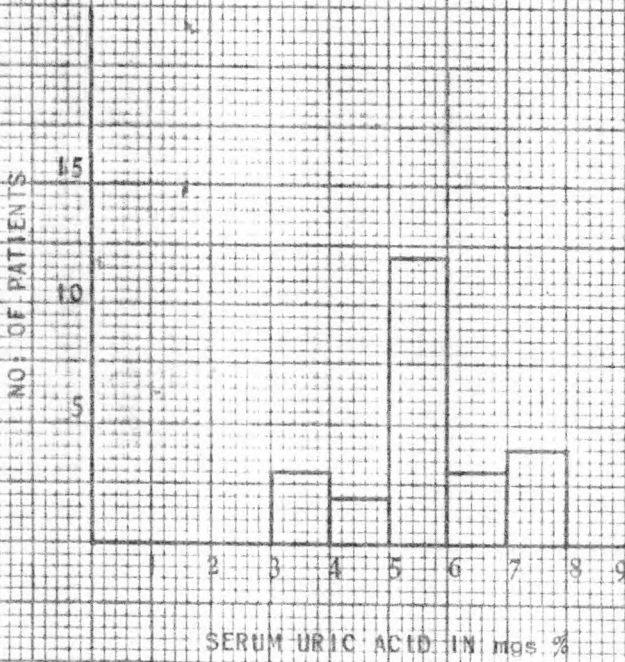


FIG: 15

SERUM URIC ACID IN 23 PATIENTS WHO HAD RECEIVED
GUANETHIDINE ALONE FOR 4 MONTHS



8. CREATININE CLEARANCE:

TABLE II:

Creatinine clearance was done for 32 patients who were admitted in the general medical wards, for control of blood pressure. 25 results were obtained and the clearance values ranged from 81mls/min to 118mls/min.

TABLE II

NO:	INITIALS:	AGE:	SEX:	SERUM CREATI- NINE mgs %	BLOOD UREA mgs%	S.U.A. mgs %	CREATININE CLEARANCE mls/min.
1	E.O.	33	M	0.6	26	6.3	98
2	P.K.	40	M	1.2	38	7.4	84
3	O.A.	51	M	0.9	22	7.4	115
4	M.K.	36	F	0.9	32	5.4	96
5	W.W.	43	F	0.7	43	6.5	93
6	M.W.	46	M	1.1	35	5.6	102
7	F.M.	59	F	0.8	24	4.9	112
8	K.K.	29	M	0.7	28	7.8	93
9	J.M.	31	M	0.8	30	6.3	110
10	F.O.	47	F	0.6	22	7.0	98
11	J.A.	38	F	1.3	27	5.6	100
12	K.M.	52	M	0.9	31	8.2	94
13	T.W.	32	F	0.5	24	3.9	105
14	W.K.	39	M	0.6	33	6.9	118
15	Z.N.	52	F	1.2	29	7.7	90
16	S.M.	29	M	0.8	34	6.2	81
17	A.W.	46	F	0.7	30	6.6	94
18	P.K.	36	F	0.8	36	5.7	87
19	E.M.	42	M	0.6	26	7.2	97
20	M.M.	57	F	1.0	40	8.1	102
21	A.M.	34	M	0.7	34	5.9	117
22	W.A.	66	M	1.1	37	8.0	89
23	D.M.	45	M	0.5	26	5.3	95
24	G.K.	50	M	0.8	36	6.5	107
25	I.W.	31	F	0.9	34	4.1	91

Key

S.U.A. SERUM URIC ACID

DISCUSSION:

Essential hypertension is amongst the commonest conditions afflicting the patients being followed in the Medical Outpatient Clinic, KNH. The fact that 67% of the patients in this study were of ages between 30 years and 50 years is in keeping with observations by other workers in this field (Abdullah, 1980). The combined incidence of hyperuricaemia in the control group was 4.8% while the incidence of hyperuricaemia in the untreated hypertensive group, 27.5%. The difference between these three incidences is statistically significant showing that hyperuricaemia is unquestionably present in a significant proportion of the essential hypertensive population.

RENAL HANDLING OF URIC ACID.

Uric acid is completely filtered by the glomeruli but most of the filtered load is reabsorbed at the proximal tubular level and the uric acid which reappears in the urine is as a result of secretion in the distal tubular system (Practorius and Kirk, (1950).

As regards the possibility that hypertension is the cause of the raised serum uric acid (SUA), it was thought that hyperuricaemia may be the result of either overproduction or under-excretion of uric acid. The best evidence of overproduction is gained from the measurement of miscible-uric acid pool size and uric turnover rate using isotope dilution methods or from studies in which the rate of incorporation of uric acid precursors, such as glycine labelled with ^{15}N , into the uric-acid pool is measured (Benedict et al, (1949)

However when 4 patients with hyperuricaemia and hypertension were studied at the Hammersmith Hospital none had evidence of overproduction of uric acid since in every case the turnover rate of labelled uric acid, measured by the rate of appearance of uric acid in the urine, was within accepted normal limits, while the size, of miscible-uric acid pool was increased (Hansen,

(1961). This would then suggest that it is a failure of excretion of uric acid that is responsible for the rise in serum uric acid in these hypertensive persons. The suggestion that it is the reduction of renal clearance of uric acid that is responsible for the hyperuricaemia in these patients is supported by the fact that even in cases of progressive renal insufficiency, hyperuricaemia does occur as a late manifestation with elevated blood urea etc preceding the development of hyperuricaemia by a wide time margin (Stele, 1967).

Further evidence of reduced uric acid clearance in the hyperuricaemic hypertensive people comes from the work of Nugent et al (1964), who found that there was no significant uric acid clearance difference between normal patients and the hypertensive patients who have normal serum uric acid. The difference between these two groups and the hypertensive hyperuricaemic patients was significant, suggesting that there is a renal tubular abnormality in the handling of uric acid, the nature of which is not clear. It is known that renal tubules are the first part of the kidney to be affected in patients with hypertension (Smith, (1951) and the finding of hyperuricaemia in these patients may be an early manifestation of the renal disorder.

In a study of 183 patients with hypertension, Kinsey et al (1961) it was found that 46% had elevated serum uric. Half of these were on benzothiazide diuretics while one third of the untreated Hypertensives had elevated serum uric acid. No correlation was found between the raised blood urea and raised serum uric acid but hyperuricaemia was commoner in those patients with severer grades of hypertension. These findings were quite consistent with the findings in my study.

AETIOLOGY

Dehydroepiandrosterone (DHA) has been shown to inhibit glucose phosphate dehydrogenase (Banks and Marks, (1960) which is the rate limiting step in the hexose monophosphate shunt. The cycle is very important for the reduction of triphosphopyridine nucleotides (TPN). Reduced (TPN) is a donor for the hydrogen ions H^+ in the synthesis of fatty acids cholesterol, phospholipids, in the reduction of S-S bonds of amino acids and also in the reduction of folic acid. Tetrahydrofolic acid, again is indispensable for the synthesis of purine bases. In order to ascertain factors influencing uric acid synthesis and blood pressure, DHA excretion in urine of hypertensive patients was studied (Kobel, (1965) and the frequency of hyperuricaemia was found much higher in DHA negative patients. The suggestion was that in DHA negative individuals there is excessive turnover of nucleic acids as there is little available reduced TPN.

De-martini (1965) demonstrated that patients with essential hypertension have high levels of lactic acid in both Venous and arterial blood, without concurrent increases in serum pyruvate . They could not correlate this finding with renal insufficiency or the various modes of anti-hypertensive therapy employed in those patients. There

were three possible explanations offered for the blood lactate pyruvate ratio:

i) peripheral vasoconstriction characteristic of hypertension may in some patients produce tissue anoxia and cause cellular metabolism to become more anaerobic.

ii) the energy required by the muscle cells to sustain vascular constriction exceeds supply of oxygen and results in greater lactate formation.

iii) the high serum lactate in some patients with arterial hypertension may reflect the increase in the work of the heart characteristic to this condition.

The high levels of serum lactate in essential hypertensive and pre-eclamptic patients has been widely implicated in the pathogenesis of hyperuricaemia in these patients (Cook 1960). In their group of patients, uric acid clearance after lactate infusion did not depend upon the changes in the glomerular filtration rate as measured by inulin and creatinine clearances. It was thought that selective changes in uric acid filtrability by lactate was unlikely and that most likely possibility was that lactate caused greater net tubular reabsorption of uric acid. This could be due to increased reabsorption of filtered uric acid and diminished tubular secretion or a combination of tubular reabsorption and secretory changes.

Ferris and Gorden (1958) showed that angiotensin II and norepinephrine do not affect arterial blood lactate but when administered at pressor doses, they still have no effect on serum lactate but reduced the renal excretion of urate and urate clearance as well. Although the relevance of a circulating pressor substance in most forms of human hypertension is yet to be defined,

it is evident that the renal haemodynamic alterations observed in hypertensive patients can be stimulated by infusion of pharmacologic doses changes observed in those acute experiments are similar to those seen in hypertensive patients, then a possible mechanism for the reduction of urate clearance occurring in many of these patients is postulated.

Wide variations of excretion of uric acid will occur in rapid alterations of extracellular fluid volume. It is suggested (Cannon & Svahn) (1970) and (Manuel & Steele (1969)), that renal urate reabsorption is a flexible parameter with altered transport activity occurring during extracellular fluid expansion or contraction. Studies have shown that renal urate clearance is decreased during extracellular fluid contraction as occurs in thiazide diuretic therapy (Wheaton et al, (1962)). This effect of extracellular fluid volume change on renal urate clearance is supported by observations in certain disease states, for example, a decrease in renal urate clearance with consequent hyperuricaemia occurs in vasopresin resistant diabetes insipidus probably due to chronic dehydration. On the other hand, hypouricaemia is consistently observed in the syndrome of inappropriate antidiuretic hormone secretion with resulting expansion of extracellular fluid volume (Mees and Assendelft, (1971)). Thus as shown above the marked shift towards hyperuricaemia seen in thiazide diuretic therapy in my study is quite consistent with observation elsewhere and it is suggested that diuretics as well as furosemide and ethacrynic

acid reduce the renal urate clearance by depleting the extracellular fluid volume. A direct effect on uric acid excretion is unlikely (Steele, (1969).

Guanethidine and alphanethyladopa did not cause any significant elevation serum uric acid as compared to the thiazide diuretic. This observation has been documented elsewhere also Fry and Barlow, (1962) and Delay and Evans (1962). It is probably due to the fact that these drugs do not cause any change in the blood lactate level nor do they affect the extracellular fluid volume. They also have no effect on renal haemodynamics while the patients is using them.

Itskovitz and Sellers (1963) observed that hyperuricaemia tends to occur in the severer grades of hypertension this has been the finding in my study as well but Breckenbridge (1966) has disputed this observation.

CONCLUSIONS:

Three conclusions can be drawn from this study:

- i) hyperuricaemia occurs in a significant population of essential hypertensive patients even without any evidence of renal impairment.
- ii) Hyperuricaemia tends to occur more commonly in the severe grades of hypertension.
- iii) Thiazide diuretic therapy does cause a marked shift towards hyperuricaemia in those patients taking them while Guanethidine and alphanethyladopa do not.

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