"ASPECTS OF SOME METABOLIC DISTURBANCES IN CHILDHOOD ACUTE LEUKAEMIA AT KENYATTA NATIONAL HOSPITAL BEFORE AND DURING THERAPY"

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A dissertation presented in part fulfilment for the degree of Master of Medicine (Paediatrics) of the University of Nairobi.

by

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1987

DEDICATION

To my late father and friend

Michael Seng'endo

Who would have been glad to read this work.

D E C L A R A T I O N:

I certify that this thesis is my own original work and has not been presented for a Degree in any other University.

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Abbreviations

ADH	–	Anti – diuretic hormone
ALL	–	Acute lymphoblastic leukaemia
AML	–	Acute myeloid leukaemia
BUN	–	Blood urea nitrogen
Ca^{2+}	–	Calcium
CAL	–	Childhood acute leukaemia
Cyto I	–	First cytoreduction
Cyto II	–	Second cytoreduction
FAB	–	French – American – British
K^{+}	–	Potassium
Mg^{2+}	–	Magnesium
Na^{+}	–	Sodium
PO_4^{3-}	–	Phosphate
PTH	–	Parathyroid hormone
SIADH	–	Syndrome of inappropriate secretion of anti-diuretic hormone

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A_B_S_T_R_A_C_T

The serum electrolytes, BUN and Uric acid of 33 patients with childhood acute leukaemia were studied before and during cytotoxic therapy over 1 year. Magnesium, calcium, inorganic phosphate and creatinine were only studied prior to induction therapy. The same parameters were studied in 66 normal controls.

Prior to induction therapy, significantly low levels of sodium, potassium, calcium and magnesium were found. Elevated levels of BUN, uric acid, inorganic phosphate and creatinine were encountered. There was no statistical difference found between data obtained in patients with ALL and those with AML.

There were changing trends in sodium, potassium, uric acid and BUN during the various phases of treatment. The most significant negative balance of sodium occurred on day 7 of induction therapy. For potassium, the lowest values were observed on days 2 and 7 in ALL and on day 14 in AML. Uric acid was elevated during induction, cytoreduction and maintenance though it showed downward trend as treatment progressed. BUN record peaks on days 2 and 7 in AML but was continuously high throughout induction therapy in ALL.

Serum albumin was found to be significantly reduced in patients as opposed to the control group.

It is recommended that urea and electrolytes should be serially determined during the induction phase of cytotoxic therapy and their disturbances should be promptly managed according to the causative factors. Uric acid levels should always be determined to assess the degree of hyperuricaemia and allopurinol should be administered during the first 21 days and this should be done from the time of diagnosis.

INTRODUCTION

Over the last decade, advances in the chemotherapy of childhood acute leukaemia have greatly improved the survival of these patients. The median survival at Kenyatta National Hospital is estimated at 15 months for Acute Lymphoblastic Leukaemia (ALL) and 8 months for Acute Myeloid Leukaemia (AML) (1). This is an improvement on the figures reported earlier by Kasili et al, who in 1978 reported a median survival of 10 months for ALL and five and a half months for AML (2). With the increasing life expectancy of these patients, attention must be focussed on those medical problems that may threaten function of vital organs and thus compromise the quality of life of these patients. Among these problems, metabolic disturbances have been frequently observed, and if recognized and corrected, the patients' prognosis could improve (3).

Hyponatraemia is probably the commonest metabolic complication encountered in AML(3). In most cases, the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) has been shown to be responsible for this phenomenon (4). In addition to SIADH, other factors have also been incriminated, for instance, saline depletion secondary to diarrhoea and vomiting, adrenal insufficiency and the inability of the kidney to

reabsorb the large osmotic load due to the lysis of tumour cells. In patients on chemotherapy, hyponatraemia has been observed where vincristine and cyclophosphamide have been used either singly or in combination with other anti-neoplastic agents, (5-9).

Hypokalaemia has most commonly been observed in AML. Its frequency seems to be so high that all patients with this disease should be routinely screened for the complication (10-11). The most important pathophysiological machanism seems to be the increased myeloid cells which contain 30-40 times the extracellular concentration of potassium (12). Other aetiological factors which have been identified include, diarrhoea and vomiting and renal losses due to lysozymuria (13-16).

Iatrogenic factors have also been incriminated in the precipitation of hypokalaemia. For example, the use of massive doses of non-absorbable anions such as penicillin, carbenicillin and nafcillin. Gentamicin, a commonly used antibiotic in these patients has also been associated with hypokalaemia (17).

Although hyperkalaemia is an infrequent complication of childhood leukaemia, it is a metabolic emergency. It causes cardiac arrhythymias such as ventricular fibrillation. Its occurence coincides with the massive lysis of neoplastic cells during induction therapy (18). It may also be due to metabolic acidosis, transfusion of aged blood and the use of potassium containing medications.

Hypocalcaemia and hyperphosphataemia are most often due toto tumour lysis in lymphoproliferative disorders. Lymphoblasts are estimated to have a phosphate concentration that is four-fold that of normal lymphocytes (19). The physiological relationship between calcium and phosphate - the solubility product- is important in the precipitation of hypocalcaemia. For instance, during tumour lysis, there is a marked elevation of phosphate. The solubility product exceeds 2 mmol/1. This leads to formation of calcium crystals in the micro-vasculature leading to hypocalcaemia and tissue damage (20,21). Other causes which have been anecdotally reported include, gram negative sepsis (22), malnutrition, steroid therapy and interference with 25, hydroxylation of Vitamin D (23)

Though reported as rare in some centres, hypercalcaemia is being increasingly recognized in childhood acute leukaemia (24-28). When severe, it can cause rapidly progressive renal failure with subsequent coma and death.

Uric acid is produced by the degredation of purines released by fragmented tumour nuclei. Like potassium and phosphate, it is primarily excreted through the kidneys. The hyperuricaemia which results, if uncorrected, leads to urate crystals to be deposited in the renal tubules. This causes an obstructive uropathy leading to oliguria and azotaemia (29).

So far, there are no conclusive reports about the role of magnesium disturbances in childhood acute leukaemia. However, significant increases in magnesium levels have been observed in adult patients (30). These suggest that magnesium, being the second most abundant intracellular cation is being released from damaged malignant cells.

To-date there have been no studies in Kenya of the metabolic disturbances that occur in childhood acute leukaemia. It is hoped that this study will throw some light on such metabolic abnormalities that are encountered in these patients and hence contribute to

their rational management. This is even more relevant when it is considered that our therapeutic protocols are different from those used elsewhere.

This study was undertaken to document any matabolic distrubances involving, sodium, potassium, blood urea nitrogen, uric acid, calcium, magnesium, serum creatinine and serum inorganic phosphate in patients with childhood acute leukaemia.

OBJECTIVES

1. To identify some of the metabolic abnormalities, if any, in childhood acute leukaemia before the commencement of therapy.

2. To determine the severity of these disturbances and any further metabolic changes during cytotoxic therapy.

3. To suggest rational approaches to the management of these disturbances.

MATERIALS AND METHODS

Study Period

A longitudinal study was carried out for one year, starting from December 1985 to December 1986.

Ethical Considerations

A written consent from the Kenyatta National Hospital Ethical Committee was obtained and a verbal consent from the parents or guardians was sought.

Study Patients

During the study, all consecutive patients admitted to Kenyatta National Hospital with a newly confirmed diagnosis of childhood acute leukaemia were recruited into the study.

All the diagnoses were classified according to the French-American-British morphological classification (appendix 1).

Controls

There were 2 controls for each patient, matched for both age and sex. These were patients who had been admitted to surgical wards for minor surgical procedures e.g. herniotomy. Blood from the controls was drawn prior to surgery.

Laboratory Methods:

After recording the patients' clinical and haematological data on a proforma (Appendix 11a and 11b), blood was drawn according the following schedule:-

i) Pre-treatment - designated as day zero
ii) During induction therapy on days 1,2,7,14,21
iii) During cytoreduction therapy on day 2
iv) At the commencement of maintenance therapy

The above intervals were based on the therapeutic protocols currently in use at the Kenyatta National Hospital i.e. protocols AL KNH/4 for ALL and protocol AL KNH/4-DAT for AML (Appendix 111).

Ten millilitres of whole blood was obtained from both patients and controls via a peripheral vein without a tourniquet. Scalp vein needles gauge No. 23 were used. The samples were collected randomly, i.e. at any time

during the day, separated immediately and the serum stored at -20 degrees centigrade. The chemical analyses were done in batches in order to avoid intra-batch variations. The Technicon SMA II auto-analyser was used for the determination of the following parameters:

i) Sodium and potassium - using the technique of Berry et al (31)

ii) Blood urea nitrogen (BUN) - after Marsh et al (32)

iii) Uric Acid - using the method of Brown (33)

iv) Albumin - by the Bromocresol-green (BCG) method (34)

v) Serum creatinine - according to Chasson et al (35)

vi) Inorganic phosphate - according to Hurst (36)

Serum calcium and magnesium were determined using the atomic absorption method. In cases where the serum albumin was below 40g/1, a correction factor, according to Payne et al (37) was used thus;

$$x = a + \frac{40 - b}{40}$$

where x = the adjusted calcium value

a = the measured calcium value

b = the albumin value

RESULTS

Patient data:

During the study period, 33 consecutive patients with a confirmed diagnosis of childhood acute leukaemia were recruited into the study. Their age and sex distribution is as illustrated in tables 1 - 3. The overall male to female ratio was approximately 2:1.

Of these patients, 22 (66.7%) had ALL and 11 (33.3%) had AML. All the 22 patients with ALL belonged to the L_2 morphological category. 7 (63.6%) patients with AML belonged to M_4, 3 (27.3%) belonged to M_3 and only 1 (9.1%) belonged to the M_2 categories respectively.

Out of the 22 patients with ALL (Fig. 1) 16 completed induction therapy, 13 completed the first cytoreduction therapy and 10 completed the second cytoreduction therapy. Only 8 patients reached the maintenance phase, the rest having died. Whereas 9 out of the 11 patients with AML (Fig. 2) completed the induction therapy, none reached the cytoreduction phase.

Table 1: Age and sex distribution of all patients with childhood acute Leukaemia (n = 33):

Age group (in years)	Male	Female	%
0 - 4	7	8	45.45
5 - 9	11	2	39.40
10 - 14	4	1	15.15
Total	22	11	100%

Table 2: Age and sex distribution of patients with ALL (n = 22)

Age group (in years)	Male	Female	%
0 - 4 yrs	6	6	54.55
5 - 9 yrs	8	1	40.90
10 - 14 yrs	0	1	4.55
Total	14	8	100%

Table 3: Age and sex distribution of patients with AML (n = 11)

Age group (in years)	Male	Female	%
0 - 4 yrs	1	2	27.28
5 - 9 yrs	3	1	36.36
10 - 14 yrs	4	0	36.36
Total	8	3	100%

Fig 2: Patient survival during study

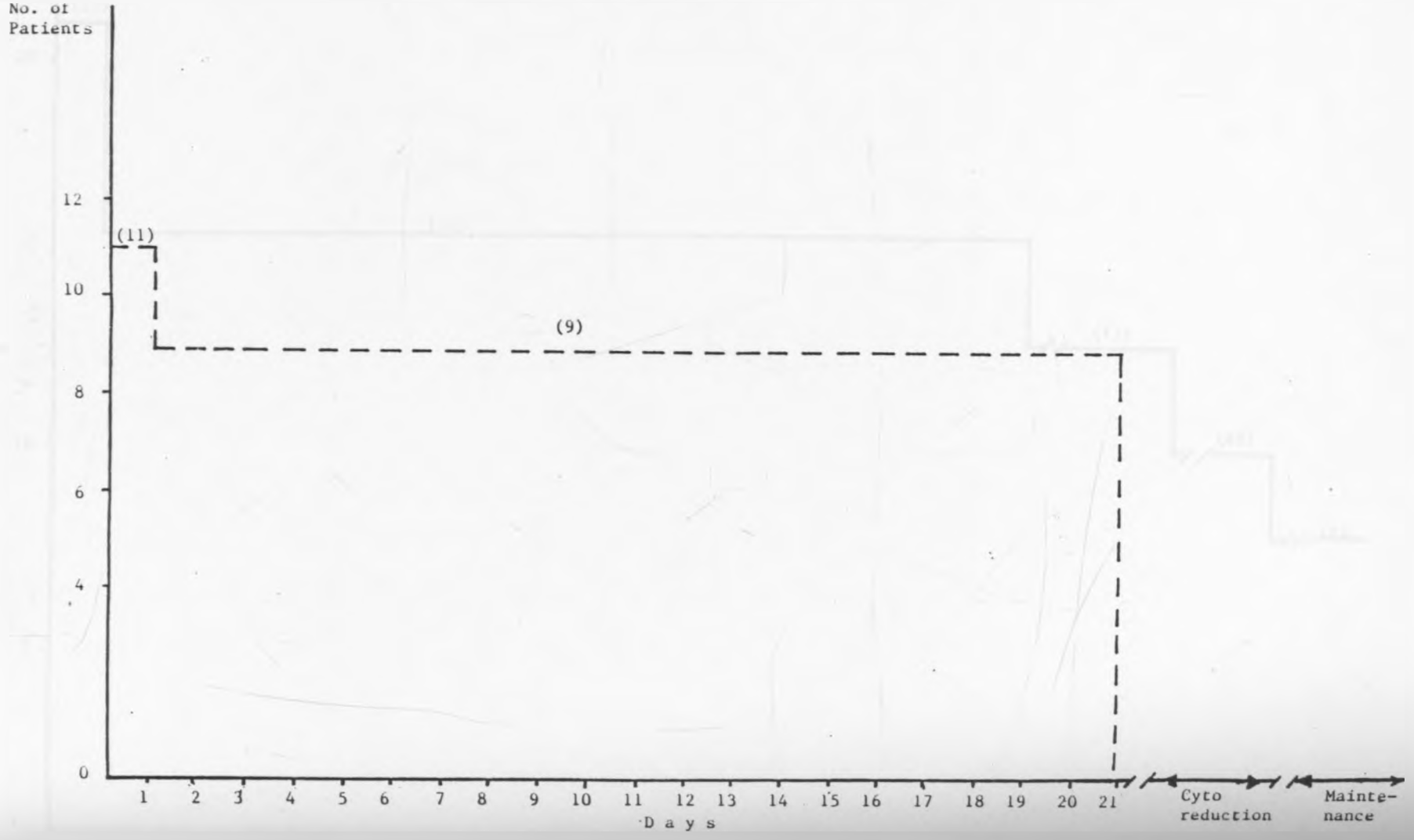
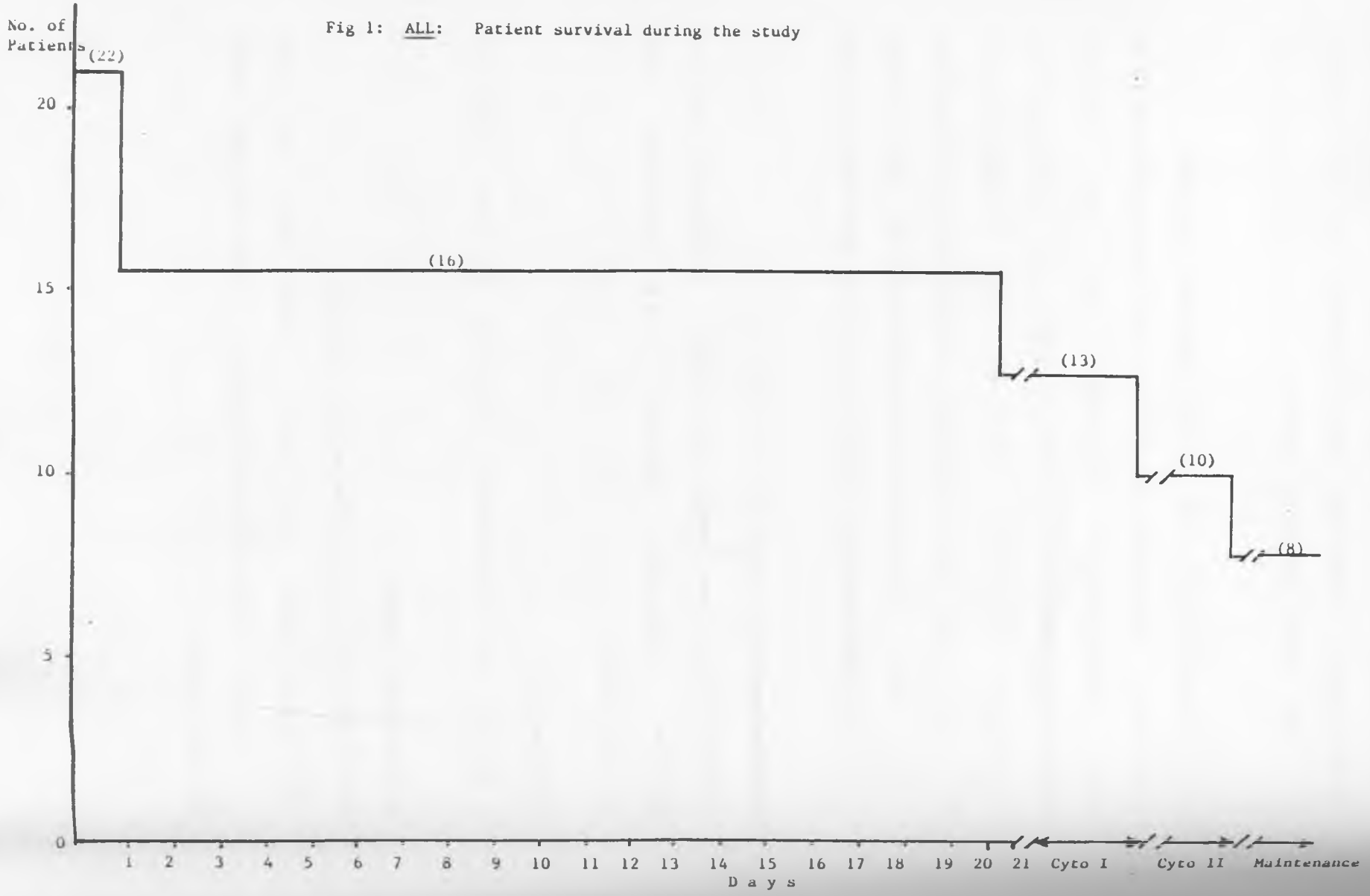


Fig 1: ALL: Patient survival during the study



Control Data:

Sixty six controls matched for age and sex were recruited into the study. Their age and sex distribution is illstrated in Table 4.

Biochemical data:

These are presented according to the phase of treatment.

i) Day zero

Before induction therapy, all patients had significantly low levels of sodium, potassium, calcium and magnesium (Table 5, $P<0.001$).

The mean sodium concentration for all patients was 128.7 mmol/l compared to 140.6 mmol/l in the normal controls. The difference was statistically significant ($P<0.001$). Patients with ALL had a mean sodium concentration of 129.2 mmol/l (Table 7). These figures were significantly different from the controls ($P<0.001$). There was no significant difference between the mean sodium values in ALL and AML ($P>0.05$).

The mean value of potassium for all patients was 3.68 mmol/l compared to 4.40 mmol/l in the normal controls (Table 5). Patients with ALL had a mean potassium level of 3.60 mmol/l (Table 6) and those with AML, 3.63 mmol/l (Table 7), both values being lower

Table 4: Age and sex distribution of controls

Age group (in years)	Male	Female	%
0 - 4 yrs	14	16	45.45
5 - 9 yrs	22	4	39.40
10 - 14 yrs	4	2	15.15
Total	44	22	100%

than in the controls ($P<0.001$) and <0.005 respectively). However, there was no significant difference between ALL and AML.

The mean calcium value for all the patients was 1.61 mmol/1 (Table 5) compared with the normal control value of 2.38 mmol/1; in ALL patients it was 1.62 mmol/1 (Table 6) and in AML 1.53 mmol/1 (Table 7). There was no statistical difference between ALL and AML.

Magnesium level was appreciably lower in patients than in controls. The mean magnesium concentration for all patients was 0.68 (mmol/l Table 5); 0.68 mmol/l for ALL (Table 6) and 0.67 mmol/l for AML (Table 7). All these values were significantly different from the control value of 0.96 mmol/l ($P<0.005$) There was no statistical difference between ALL and AML.

The patients' blood urea nitrogen, uric acid, inorganic phosphate and creatinine were all significantly elevated on day zero compared to the controls ($P<0.001$).

Uric acid was elevated in both groups of leukaemics. The mean serum uric acid in patients with leukaemia was 318.2 umol/l compared to 193.3 umol/l in the controls (Table 5). The mean serum uric acid in ALL was 316.1umol/l (Table 6) and 322.6 umol/l in AML. There was no statistical difference between ALL and AML patients ($P > 0.05$). However, there was a wide scatter in the uric acid readings observed in patients (2SD = 101.64 umol/l). This appeared to be related to the white blood cell counts and indeed there was good correlation between the 2 variables (Fig.3) ($r = 0.72$; $P<0.001$).

Fig 3: The relationship between Uric acid and white blood cell counts

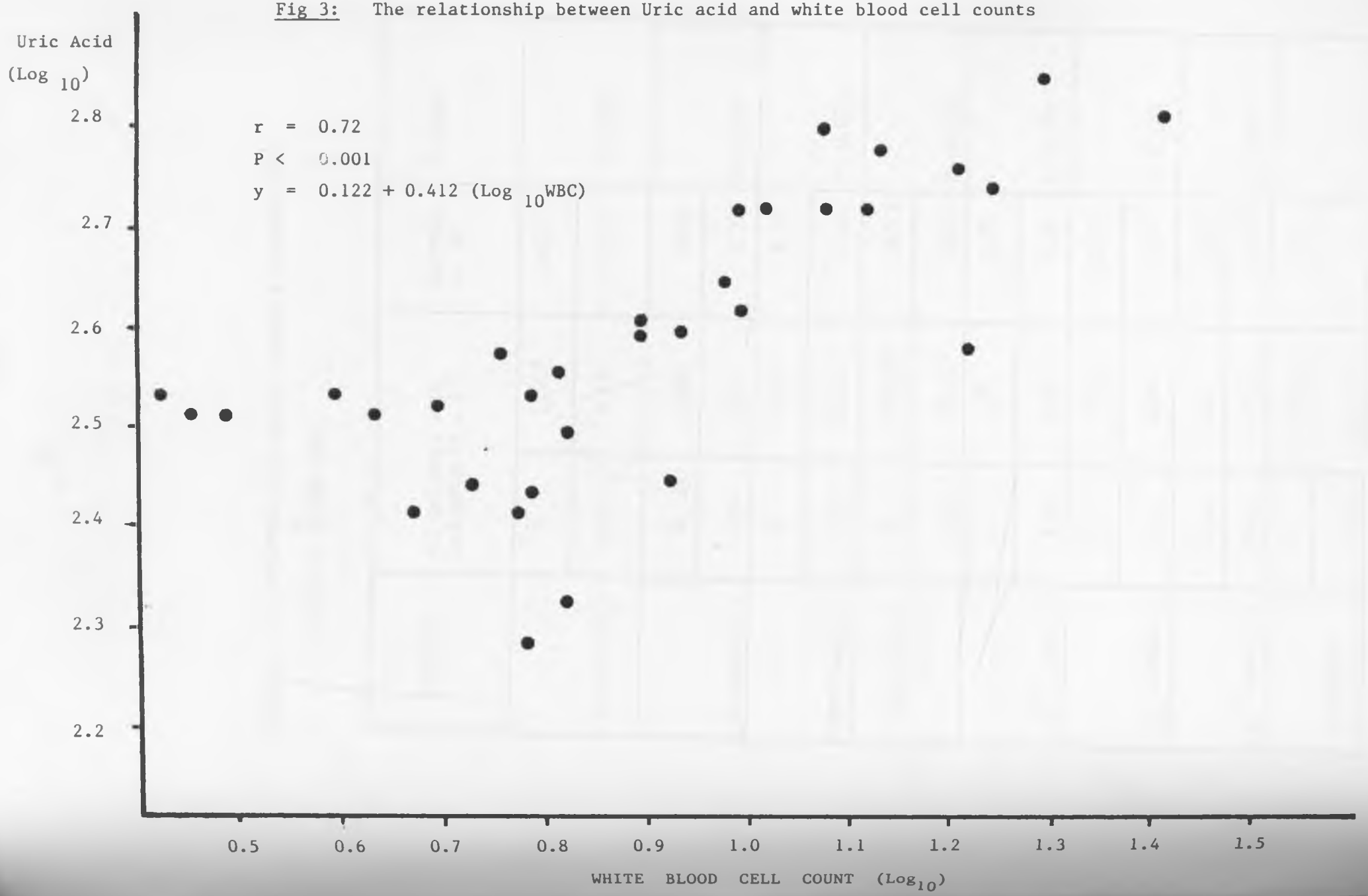


Table 5: All patients with acute leukaemia compared with controls on day zero.

Variable	All patients with leukaemia (n = 33)		Controls n = 66	P Value
Na^+(mmols/l)	$\bar{X}$	128.7	140.6	P< 0.001
	S.D.	7.63	6.2	
K^+ (mmols/l)	$\bar{X}$	3.68	4.40	P< 0.001
	S.D	0.78	0.78	
BUN (mmols/l)	$\bar{X}$	4.25	3.36	P< 0.001
	S.D.	1.55	1.61	
Uric Acid µmol/l	$\bar{X}$	318.28	193.3	P< 0.001
	S.D.	101.64	20.1	
Ca^{2+} (mmol/l)	$\bar{X}$	1.61	2.38	P< 0.001
	S.D.	0.27	0.81	
PO_4^{3-}(mmol/l)	$\bar{X}$	2.28	1.58	P< 0.001
	S.D.	0.54	0.49	
Mg^{2+}(mmol/l)	$\bar{X}$	0.68	0.96	P< 0.001
	S.D.	0.12	0.11	
Creatinine (umol/l)	$\bar{X}$	72.45	55.1	P< 0.001
	S.D.	35.77	13.7	

Table 6: Patients with ALL compared with the controls on day zero

Variable	Patients (n = 22)		Controls (n = 66)	P Value
Na^+ mmol/l	$\bar{x}$	129.20	140.6	P< 0.001
	S.D.	6.91	6.2	
K^+ mmol/l	$\bar{x}$	3.60	4.4	P< 0.001
	S.D.	0.71	0.78	
BUN mmol/l	$\bar{x}$	4.64	3.36	P< 0.001
	S.D.	1.69	1.61	
Uric Acid µmol/l	$\bar{x}$	316.10	193.3	P< 0.001
	S.D.	94.24	20.1	
Ca^{2+} mmol/l	$\bar{x}$	1.62	2.38	P< 0.005
	S.D.	0.31	0.61	
PO^{3-} mmol/l	$\bar{x}$	2.42	1.58	P< 0.001
	S.D.	0.56	0.49	
Mg^{2+} mmol/l	$\bar{x}$	0.68	0.96	P< 0.001
	S.D.	0.12	0.11	
Creatinine µmol/l	$\bar{x}$	72.14	55.1	P< 0.001
	S.D.	39.82	13.7	

Table 7: Patients with AML compared with controls on day zero

Variable	Patients (n = 11)		Controls (n = 66)	P Value
Na^+ mmol/l	$\bar{x}$	127.7	140.6	
	S.D.	8.82	6.2	P< 0.005
K^+ mmol/l	$\bar{x}$	3.63	4.40	
	S.D.	0.97	0.78	P< 0.005
BUN mmol/l	$\bar{x}$	3.47	3.36	
	S.D.	0.78	1.61	P< 0.005
Uric Acid µmol/l	$\bar{x}$	322.6	193.3	
	S.D.	114.90	20.1	P< 0.005
Ca^{2+} mmol/l	$\bar{x}$	1.53	2.38	
	S.D.	0.17	0.81	P< 0.005
PO_4^{3-} mmol/l	$\bar{x}$	2.02	1.58	
	S.D.	0.35	0.49	P< 0.001
Mg^{2+} mmol/l	$\bar{x}$	0.67	0.97	
	S.D.	0.12	0.11	P< 0.005
Creatinine µmol/l	$\bar{x}$	73.1	55.1	
	S.D.	25.8	13.7	P<0.005

The patients' mean inorganic phosphate was 2.28 mmol/l (Table 5) against the control of 1.58 mmol/l. The mean values were 2.42 mmol/l for ALL (Table 6) and 2.02 mmol/l for AML Table 7). While these figures were significantly diiferent from the controls, no significant difference was observed between ALL and AML.

The overall mean value of creatinine in patients was 72.45umol/l against the controls of 55.1umol/l (Table 5). The respective values in ALL and AML were 72.14umol/l (Table 6) and 73.1umol/l (Table 7), showing no obvious difference.

Hypoalbuminaemia was observed in 78.6% of patients. Their mean albumin value being 31.6g/l as compared to the control of 39.2g/l. The difference was statistically significant ($P<0.005$).

ii) Induction phase

It is observed that these biochemical parameters showed changing patterns during induction therapy and their changing trends exhibited deviations from the mean values of day zero. For instance, sodium dropped

to a nadir on day 7 (Figure 4) in both ALL and AML, while the potassium level was lowest on the 14 day in ALL patients ($P<0.05$; Fig 5). the two lowest observations of potassium in AML patients occurred on days 2 and 14 ($P<0.05$; Figure 5).

Uric acid levels rose on days 1 and 2 in both ALL and AML patients (Figure 6), then gradually dropped and by day 21 both groups had significantly lower levels than was recorded on day zero ($P<0.05$; Figure 6)

BUN significantly rose on days 2 and 7 in AML ($P<0.05$; Figure 7) but in ALL both negative and positive changes occurred during induction therapy. The latter changes remained significant throughout the induction therapy ($P<0.05$; Fig. 7).

iii) Cytoreduction phase for ALL:

During the first cytoreduction course for ALL (Table 8) the mean sodium value was 133.8mmol/l compared to the control value of 140.6mol/l. The difference was statistically significant ($P < 0.005$. The mean potassium value was 4.26mmol/l compared to the control value of 4.40mmol/l. this difference was not statistically significant ($P > 0.05$. The patients' BUN value of 4.69mmol/l was statistically different from that of controls of 3.36mmol/l ($P < 0.001$). Serum uric

Fig 4: Deviations from day 0 during induction therapy

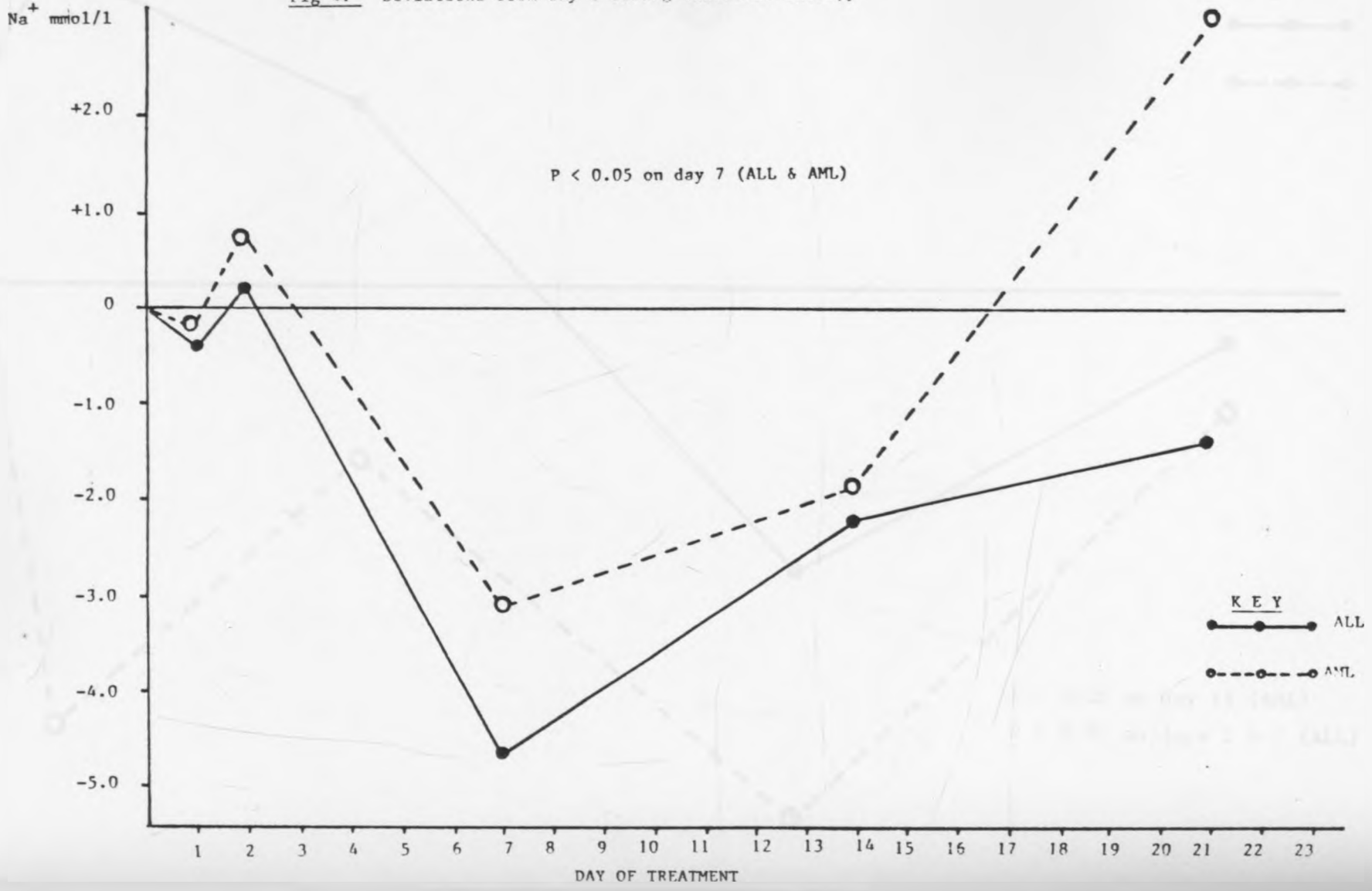


Fig 5: K^+ Deviations from day 0 during induction therapy

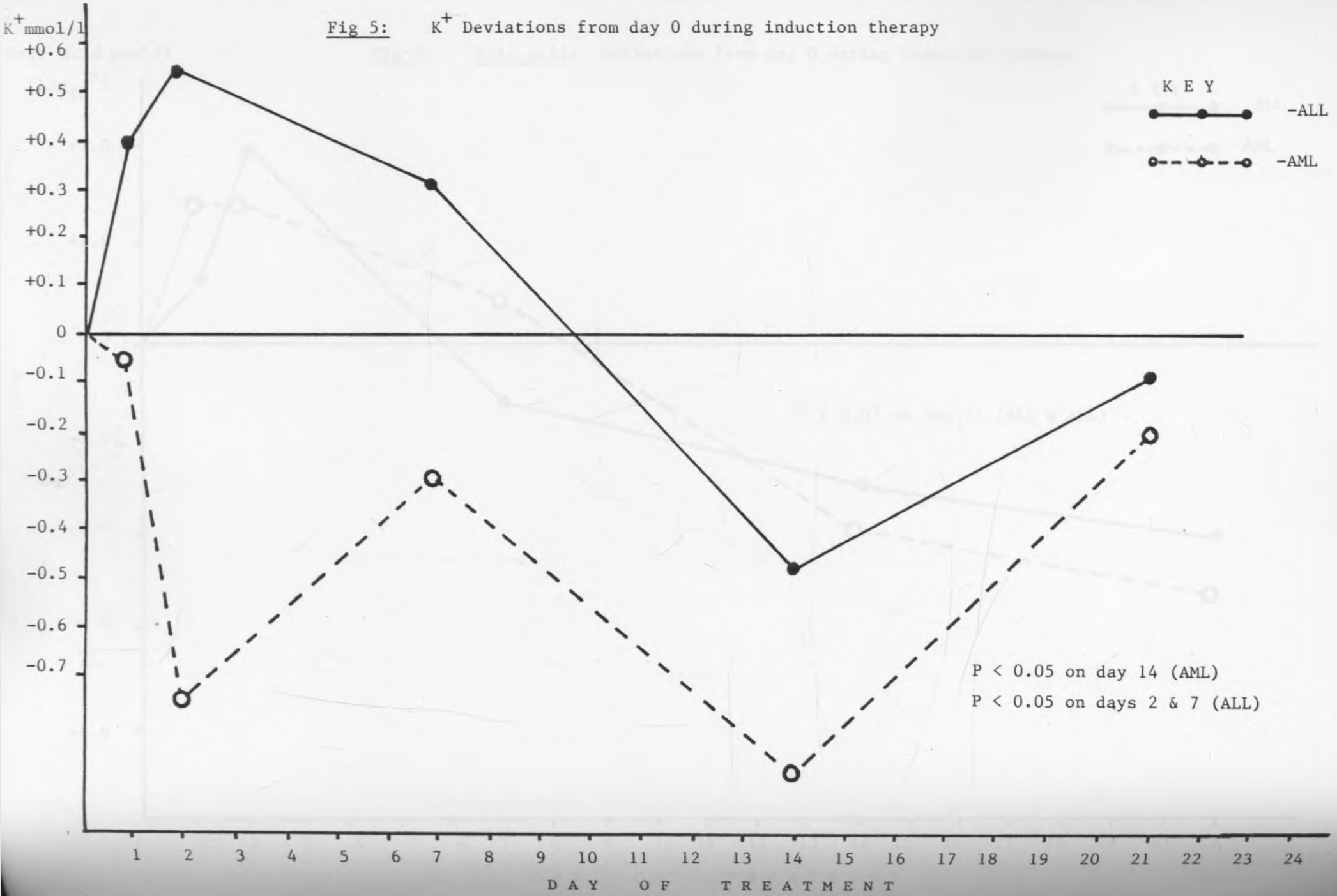


Fig 6: Uric acid: Deviations from day 0 during induction therapy

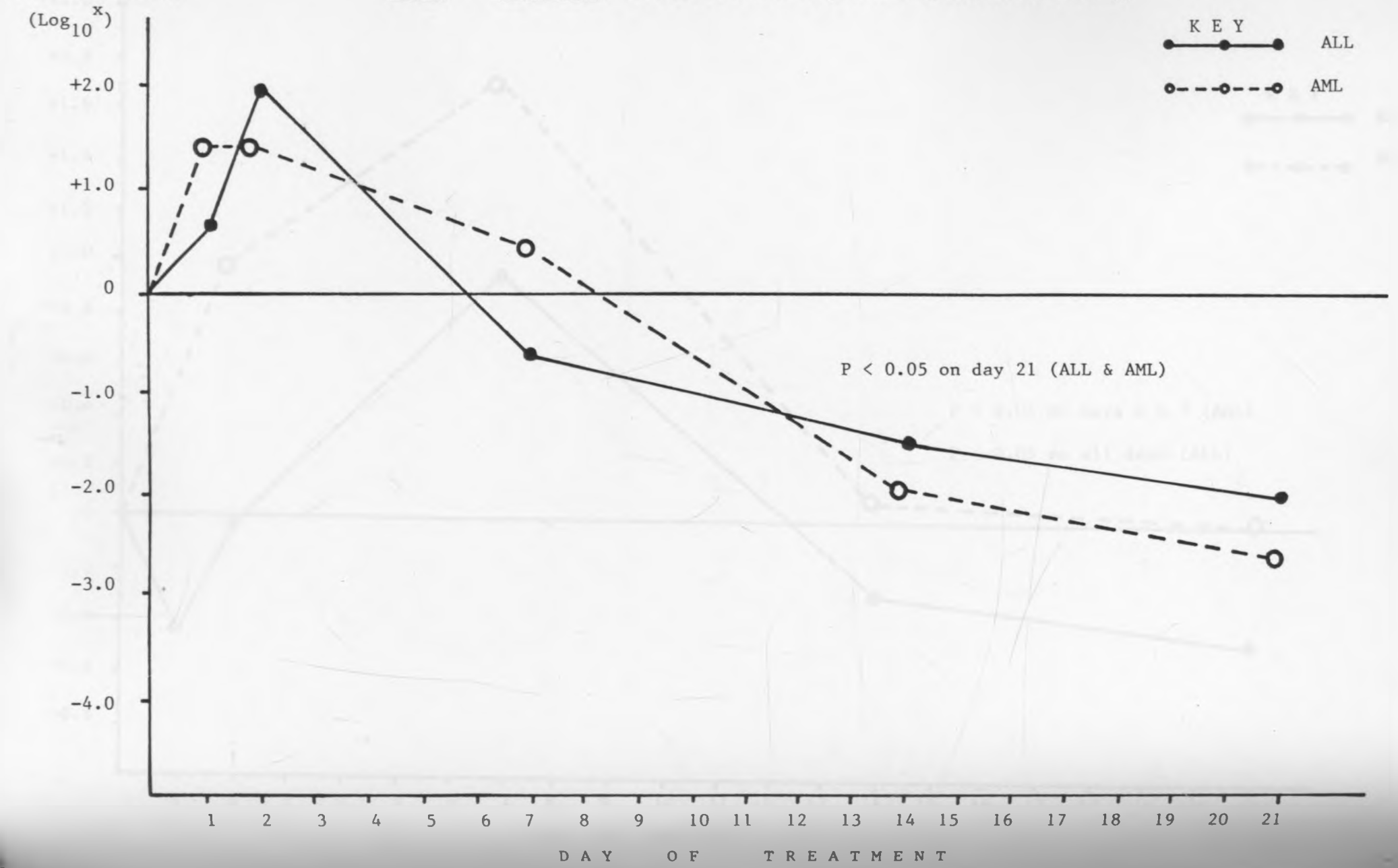
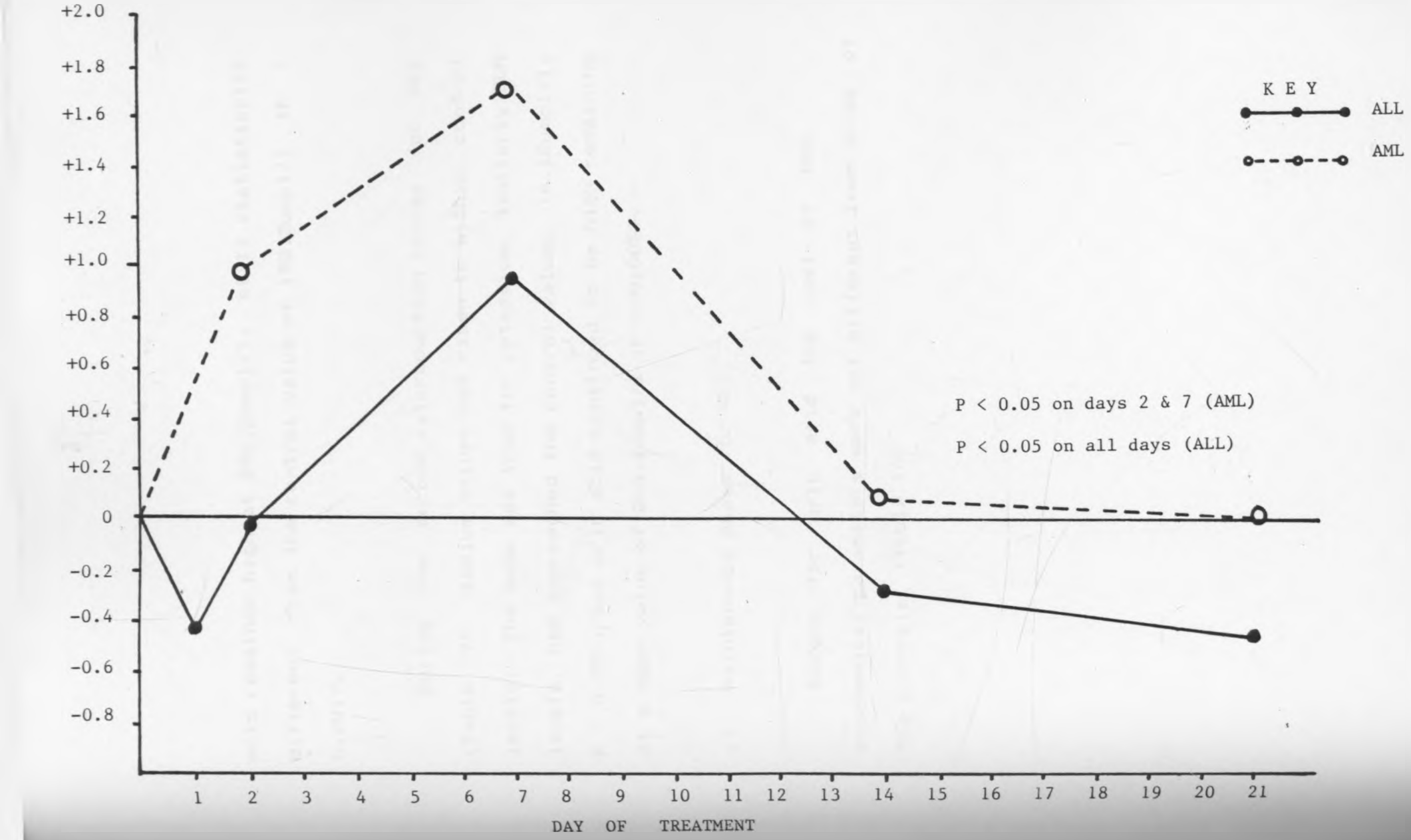


Fig 7: BUN: Deviations from day 0 during induction therapy



acid remained high at 292.3umol/l, still statistically different from the control value of 193.3umol/l ($P < 0.001$).

During the second cytoreduction course for ALL (Table 9) sodium va;ues had risen to within control levels. The same was true for potassium. Similarly BUN levels had approached the control values (4.12umol/l: $P < 0.05$), but uric acid continued to be high remaining at a mean value of 244.1umol/l ($P < 0.005$).

v) Maintenance phase for ALL

Except for uric acid the rest of the biochemical parameters were not different from those of the controls. (Table 10)

Table 8: Mean values of Na^+, K^+, BUN and uric acid in patients with ALL during cytoreduction I:

Variable	Patients with ALL (n = 13)	Controls (n = 66=	P value
Na^+ mmol/l	133.8±5.10	140.6±6.2	P < 0.005
K^+ mmol/l	4.26±0.81	4.40±0.78	P >0.05
BUN mmol/l	4.69±0.95	3.36±1.61	P <0.0 01
Uric acid µmol/l	292.3±31.3	193.3±20.1	P <0.001

Table 9: Mean values of Na^+, K^+ BUN and uric acid in patients with ALL during cytoreduction II

Variable	Patients with ALL n = 10	Controls n = 66	P value
Na^+ mmol/l	139.2 ± 4.9	140.6 ± 6.2	P > 0.05
K^+ mmol/l	4.28 ± 0.31	4.40 ± 0.78	P > 0.05
BUN mmol/l	4.12 ± 0.37	3.36 ± 1.61	P > 0.05
Uric acid µmol/l	244.1 ± 19.9	193.3 ± 20.1	P < 0.005

Table 10: Mean values of Na^+, K^+, BUN and uric acid in patients with ALL during maintenance therapy.

Variable	Patients with ALL n = 8	Controls n = 66	P value
Na^+ mmol/l	138.1 ± 5.0	140.6 ± 6.2	P > 0.05
K^+ mmol/l	4.19 ± 0.44	4.40 ± 0.78	P > 0.05
BUN mmol/l	3.78 ± 0.28	3.36 ± 1.61	P > 0.05
Uric acid µmol/l	224.3 ± 22.8	193,3 ± 20.1	P < 0.005

DISCUSSION

Alterations in the normal physiologic regulations of many systems occur in leukaemia. These include biochemical disturbances observed in these diseases. Serial studies of these disturbances during the various phases of therapy are scanty. This discussion attempts to account for such abnormalities observed during this study.

Sodium:

Hyponatraemia is probably the commonest complication encountered in AML (3). In one study (3) hyponatraemia was observed in 11 out of 14 patients studied. In the present study, the mean sodium value for patients with AML on day zero was 127.7 mmol/l (Table 7), the control mean being 140.6mmol/l. Sodium values were thus significantly low. In ALL patients a mean sodium value of 129.2 mmol/l on day zero (Table 6), was not statistically different from that of AML patients.

Among the various reasons advanced to explain the occurrence of hyponatraemia in childhood acute leukaemia has been SIADH for example in patients studied by Mir and Delamore (3). In another report, water balance studies done on 42 patients confirmed the presence of features of SIADH (4). In this study it is

difficult to assess the contribution of this syndrome because water balance studies were not done. During induction therapy, both ALL and AML patients exhibited a slight rise in the sodium on day 2 (Figure 3). This rise could be due to the multiple blood transfusions in our patients prior to commencing cytotoxic therapy. On the other hand, on day 7 there was a significant drop in the sodium level. This change may have been due to a number of factors, but gastrointestinal losses through emesis induced by cytotoxic agents used in the treatment of both ALL and AML could have also had a role. Vincristine sulphate, important in the remission induction of ALL has been documented as a cause of hyponatraemia (5-8). In the 8 cases reviewed by Stuart et al (7), vincristine induced hyponatraemia within 4 - 10 days of its administration. They also further showed that increased ADH secretion following repeated challenge with vincristine is a reproducible finding. In 2 of their patients serum ADH levels were markedly elevated during the hyponatraemic period. It is of significance in this respect, to note that in the present study the lowest sodium values occured on the 7th day after initiation of therapy. The hyponatraemia observed on days 14 and 21 may partly be a result of continued administration of vincristine in our protocol.

Cyclophosphamide in high doses (1200mg/m^2) is part of our remission induction regimen for AML (appendix III). It is administered as a single intravenous infusion on day 6. Although reported to have no nephrotoxic effect (9) cyclophosphamide in high doses impairs water excretion. It precipitates hyponatraemia with inappropriately concentrated urine, decreases urine flow and weight gain. In studies by Defronzo et al (9), the development of this syndrome correlated temporarily with the appearance of alkylating metabolites of cyclphosphamide in urine and serum. The half-life of cyclophosphamide has been estimated to be 6 - 7 hours (38). In contrast, peak anti-duretic effect occurs 10 - 14 hours after cyclophosphamide administration. It is probable that the significant difference observed in sodium on day 7 could have been partly due to cyclophosphamide administration. Thereafter sodium values gradually rose and by day 21 they were back to pre-treatment levels. On the second day of the first cytoreduction of ALL, the mean sodium value was 133.8 mmol/l (Table 9). This low value could be partly accounted for by the administration of high dose cyclophosphamide as an infusion on day 1 of cytoreduction. Also, gastrointestinal losses may have been an added contributory factor through the marked emetic effect of this drug.

During the second cytoreduction course and maintenance phase in ALL the mean sodium value had risen to be comparable to control levels. The explanation for this rise during the second cytoreduction and maintenance therapy could be that the surviving patients' tumour burden had been markedly reduced, gastrointestinal losses were minimal and the cyclophosphamide was reduced in both dosage and frequency of administration.

Potassium

The day zero values of potassium were significantly lower in patients than controls ($P<0.001$; Table 5 - 7). Unexpected hypokalaemia is a frequent complication of AML. Studies of hypokalaemia in acute leukaemia were initially in patients with AML (11). Later on, hypokalaemia was also reported in ALL. There may be many factors underlying this observation. Immature cells are thought to have an increased uptake of potassium (12) and this per se contributes to hypokalaemia in acute leukaemia. Renal losses of potassium in AML has been attributed to lysozymuria (13-16). Finch, Gnabasic and Rogoway (40) and Jolles et al (41) were the first to report an increased serum level of lysozyme (muramidase) in monoblastic (FAB-M5) and myelomonocytic leukaemia (FAB-M4). Osserman, Lawlor

and others (42), further noted hyperkaluria in patients with AML FAB category M4. Excessive excretion of portassium was also noted in some patients by Muggia et al (13). Kasili, Orinda and Mudasia (16) demonstrated the elevation of serum lysozyme level in AML FAB M4 and M5 in Kenyan Africans.

There is evidence that high concentrations of lysozyme may damage the proximal tubular cells in the kidney (43). This renal lesion then leads to the tubular leak of potassium. In this study, 7 out of 11 patients with AML belonged to FAB - M4. Though their serum lysozyme levels were not estimated, inferring from the study of Kasili et al (16), it is possible that the 7 patients had elevated levels which could have contributed to hypokalaemia and kaliuresis.

Young and others (17) reported the occurrence of hypokalaemia in patients with acute leukaemia treated with a combination of gentamicin and cephalexin. An earlier study by Tattersall et al (44) had showed that a series of patients with blood dyscrasias, developed hypokalaemia while on multiple antibiotic therapy which included gentamicin and cephalexin. These authors attributed the hypokalaemia to transcellular movement of potassium and increased renal potassium excretion. During this study, a number of patients developed infection for which they received a combination of

gentamicin and a penicillin as the first line antimicrobial therapy. It is not possible to quantitate the role played by these antibiotics but they may have contributed to the severity of hypokalaemia.

Prednisone therapy has been recognized as a factor in potassium renal wasting (45). Our protocol for ALL includes predinisone ($40mg/m^2$) daily for 6 weeks and its contribution to the hypokalaemia observed in ALL cannot be underestimated. Lastly, another factor important in the hypokalaemia may have been gastro-intestinal losses due to vomiting. The frequency of vomiting was, however, not assessed during the study.

Patients with AML exhibited lower values of potassium during the first 21 days of induction therapy (Fig.4). This difference could be attributed to better renal handling of potassium by ALL patients and the higher levels of serum lysozyme in AML patients. During the cytoreduction and maintenance phases of ALL, the potassium levels had risen to normal levels (Tables 7,9, and 10). This normalization is due to amelioration of the factors discussed that were operative before and during initial therapy.

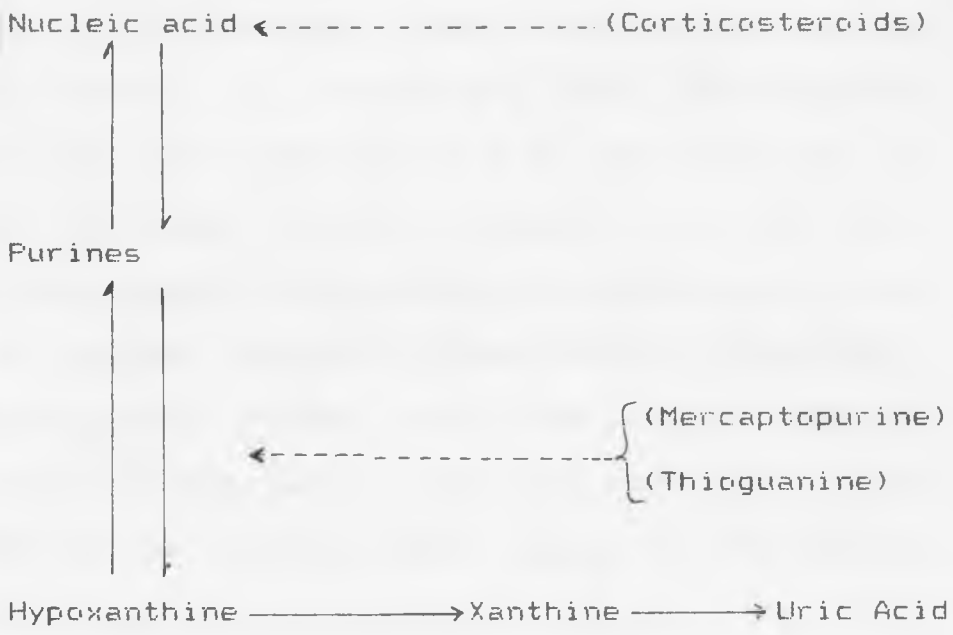
Uric Acid:

Prior to treatment, the mean value of uric acid for ALL and AML patients was 318.3umol/l compared to 193umol/l in controls (Table 5). The difference was significant ($P<0.001$). There was no statistical difference between ALL and AML.

There was a wide variation in the uric acid readings observed amongst patients. This variation appears to have been related to pre-treatment white blood cell Count (fig. 7). There was good correlation between cell count ($r=0.72$; $P<0.001$). This finding confirms the observation by Sandberg et al (46), that there is a correlation beteen uric acid concentration in plasma and urine and the total white blood cell counts.

A marked elevation in serum uric acid level has been frequently observed in adults with certain forms of neoplastic disease (47,48). Prior to a report by Holland and others (49), hyperuricaemia was reported as rare in CAL. In their report of 5 patients with ALL, severe hyperuricaemia was observed in 3 patients prior to cytotoxic therapy. In the present study the mean uric acid before cytotoxic therapy for ALL was 316.1umol/l which was significantly elevated compared to controls ($P<0.001$). Krakoff (29) studied changes in uric acid in patients with leukaemia treated with

various chemotherapeutic agents. From his study he inferred that purine analogues (6-Mercaptopurine and Thioguanine) increased uric acid production by interrupting nucleic acid synthesis after the formation of hypoxanthine ribotide.



On the other hand, corticosteroids produce a rise in uric acid secondary to an increased degradation of nucleic acids rather than an interruption in their synthesis.

In our protocols, prednisone is used in the remission induction of ALL, whereas thioguanine is used in the remission induction of AML. Both agents are known to increase serum uric acid levels as indicated above.

My findings, therefore, agree with observations by other workers (50,51) that there is a tendency to hyperuricaemia following rapid cell lysis by effective chemotherapeutic agents.

Allopurinol, which is a xanthene oxidase inhibitor, blocks the conversion of hypoxanthine and xanthine to uric acid. It is routinely used in our protocol during cytotoxic therapy. It is possible that the gradual decline in uric acid with time (Fig 5) was partly due to the use of this drug. It should, however, be noted that none of the patients in the study developed acute renal failure as has been reported by some workers (47,49,52). The significantly raised uric acid levels during cytoreduction II (244.1umol/l) may have been due to the rapid lysis of the residual tumour cells. As the tumour burden decreased during maintenance therapy, the uric acid levels correspondingly decreased.

Calcium, Phosphates and Magnesium:

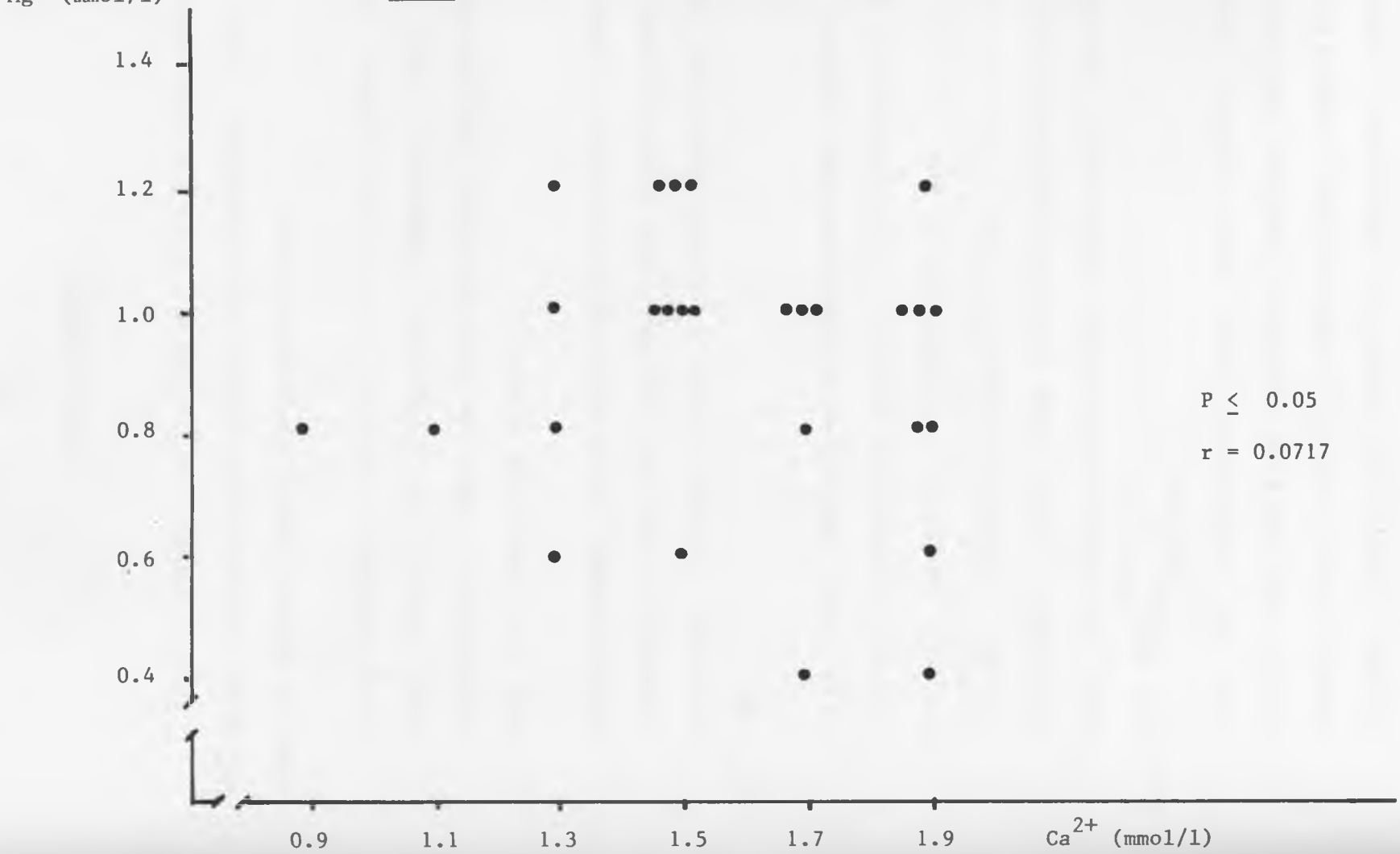
Until 1972, hypocalcaemia was thought to be infrequent in childhood acute leukaemia, when Jaffe et al (20) reported 16 episodes of hypocalcaemia in 10.4% of children hospitalized for acute leukaemia. Normal calcium homeostasis is maintained by several mechanisms. Among these are the reabsorption of bone, the renal excretion of calcium and phosphate, the gastrointestinal absorption of calcium and the distribution of calcium and phosphate in the body fluids and tissues. Any interference or abnormality with these mechanisms may result into hypocalcaemia or vice-versa. In this study several mechanisms may have been operative. For instance, hypoalbuminaemia was present in 78.6% of patients. This could have accounted for a reduction in the serum calcium. The hypoalbuminaemia was probably secondary to hypercatabolic states due to infection, hepatic dysfunction, failure of absorption or losses via the gastrointestinal tract. Hyperphosphataemia is another factor that could be incriminated in the hypocalcaemia that was observed. The phosphorous load may have come from lymphoblasts which are known to contain four-times the amount of organic phosphorus compared to mature lymphocytes (53). Although urinary calcium loss and tubular reabsorption of phosphorus were not measured, the increased uric acid, BUN and creatinine are

indicative of some degree of renal compromise probably secondary to the increased uric acid deposition in the kidneys (54).

In the absence of parathyroid hormone (PTH) determinations, magnesium concentrations were assayed and their mean values were lower in patients with CAL than in the controls. Although there was a high association between magnesium and calcium levels (Fig 8), there was no direct correlation between the two elements. This is reflection of the heterogeneity in the causes of hypomagnesaemia. Chase and Slatopolsky (55), suggest that magnesium depletion impairs bone calcium-magnesium exhange and later suppresses PTH secretion to maintain the hypocalcaemia. The persistently low levels of magnesium in patients studied could possibly have led to hypocalcaemia through PTH suppression.

An important factor that could have contributed to the observed hypomagnesaemia through increased renal wasting of magnesium and potassium due to secondary hyperaldosteronism induced by gentamicin therapy (56,57). As mentioned earlier, gentamicin is frequently used to treat infection in our patients. Therefore, it is feasible that it contributed to the low magnesium levels observed in this study by inducing hyperaldosteronism.

Fig 8: The relationship between Magnesium and Calcium



CONCLUSIONS:

This study has demonstrated that bio chemical changes outlined below occur and an attempt has been made to discuss their pathophysiology.

1. Hyponatraemia occured in both ALL and AML before the start of induction therapy. The most significant negative balance being noticeable on day 7 of induction therapy.

2. Hypokalaemia occurred before and during induction therapy in both ALL and AML. The lowest values were observed on days 2 and 14 in ALL and on day 14 in AML.

3. Uric acid was significantly elevated before the start of cytotoxic therapy. It continued to be so during induction, cytoreduction and maintenance, though it showed a downward trend in the course of treatment. There was a direct correlation between the uric acid and the total white cell counts on day zero.

4. BUN and creatinine were significantly elevated before the start of cytotoxic therapy. BUN recorded peaks on day 2 and 7 in AML and was significantly higher than the controls throughout induction therapy in ALL.

5. Magnesium and calcium were significantly low before treatment.

6. There was a strong association but no direct correlation between magnesium and calcium levels before therapy.

7. Hyperphosphataemia was present before starting cytotoxic therapy.

8. Hypoalbuminaemia was observed in a significant percentage of patients before the start of treatment.

R E C O M M E N D A T I O N S

From the results and conclusions of this study, the following are recommended:-

1. Water balance studies should be carried out in order to assess the occurrence of SIADH in our patients.

2. Sodium should be determined serially from day zero to day 21 of induction therapy with particular attention being paid on day 7. This will enable one to recognize profound disturbances and correct them in time. The hyponatraemia that occurs should be treated according to the cause.

3. Potassium levels should be watched closely particularly on day 2 and 7 in ALL and on day 14 in AML. Standard measures of treatment of hypokalaemia should then be instituted when it occurs.

4. In order to avert unexpected acute renal failure renal function studies should be done in the patients before and during cytotoxic therapy.

5. Hyperuricaemia should be looked out for. Allopurinol should be given to these patients from the time of diagnosis. From this study it is possible to suggest that allopurinol should be administered during the first 21 days of induction therapy only.

6. Although not studied serially, hypoalbuminaemia occurred significantly in patients prior to the start of treatment. A high protein diet should be given to these patients during their hospital stay.

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APPENDIX 1:

FAB Classification of the Acute Leukaemias

1. Acute Lymphoblastic Leukaemia (ALL)

   L1 - Small uniform monomorphic Lympholasts.

   L2 - Large heterogeneous lymphoblasts.

   L3 - Burkitt's Cell type.

2. Acute myeloid leukaemia (AML)

   M1 - Myelobastic (without maturation beyond the blast).

   M2 - Myelobastic (with maturation to myelocytes and other maturer forms)

   M3 - Promyelocytic

   M4 - Myelomonocytic (myelobasts and monoblasts present)

   M5 - Monocytic

   M6 - Erythroleukaemia (DiGulglielmo's disease)

* (From Bennet et al. Brit. J. Haemat. 33: 451, 1976).

APPENDIX IIa

PROFOMA

Name:---------- Sex:---------- Age:------ IPNO.:-------

Address: ---------- Date: ----------

Diagnosis : ----------

Stage of therapy: --------- Pre Rx/Induction/Cytoreduction
I or II/Maintenance.

Clinical Assessment

	Yes	No
Pallor	------	-----
Lymphadenopathy	------	-----
Jaundice	------	-----
Petichiae	------	-----
Echymoses	------	-----
Purpura	------	-----
Choloromata	------	-----
Gingival hypertrophy	------	-----
Bone tenderness	------	-----
Splenomegaly	------	-----
Hepatomegaly	------	-----
Mediastinal mass	------	-----

	Yes	No
Pul. inflitrates/effusion	------	------
Gonadal infiltrates	------	------
Priapism	------	------
Pericarditis	------	------
Proptosis	------	------
Meningitis	------	------
Cranial nerve palsies	------	------

APPENDIX IIb

PROFORMA III

Name : ---------- Sex: --------- Age : ------ IP No: -----

Address : ---------- Date : ----------

Stage of therapy: Day 0,2,7,14, 21 cyto I, Cyto Ii, Maintenance

WBC: Total ----------

Diff. - N - % - E - % -M - % - B - % - Blasts - %

Platelet count : ----------

Na+ : ---------- K+ ----------

BUN : ----------

Serum Albumin : ----------

Serum Ca^{2+} : ----------

Serum Ca^{2+} : ----------

Inorganic phosphate : ----------

Serum creatinine : ----------

Serum magnesium : ----------

Serum uric acid: ----------

Chest X-ray/

Skeletal Survey : ----------

APPENDIX III

PROTOCOL: AL KNH/4 for acute lymphocytic Leukaemia.

i). Induction.

- Vincristine - 2 mg/m^2 I.V. Weekly for 4 weeks.

- Predinisone - 40 mg/m^2 orally in 3 divided doses daily, tailing off in week 6.

Depending on whether there is bone marrow remission or not, a further dose of Vincristine could be given or after a week's rest start;

ii). Cytoreduction (Two courses)

- Adriamycin 30mg/m^2 I.V. (Day 1 - 3)
  To be omitted in the second course of cytoreduction.
- Cyclophosphamide - 1200mg/m^2 I.V. given in saline infusion on day 1.
- Cytosine arabinoside - 100mg/ m^2 I.V. daily as I.V. Push on day 1 to 5 or Methotraxate 20mg/m^2 daily on day 1 - 5.

iii) Maintenance

(to start after one week's rest and continue for 24 months).

- 6 - Mercaptopurine - 75mg/m^2 orally daily.

- Methotraxate - 15mg/m^2 orally weekly.

- Vincristine - 1mg I.V. monthly.

- Prednisone - 40mg/m^2 orally in 3 doses daily x 7 days monthly.

- Adriamycin - 40mg/m^2 every 3 months.

- Cyclophosphamide - 400mg/m^2 I.V. every 3 months.

i) Induction/cytoreduction

- Daunorubicin - 40mg/m^2 I.V. on days 1 - 3

- Cytosine Arabinoside - 100mg/m^2 I.V. twice daily on days 1 - 6.

. Thioguanine - 80mg/m^2 (or 6 -MP - 100mg/m^2) orally on days 1 - 6.

. Cyclophosphamide - 120mg/m^2 in saline infusion day 6 only.

* The pulse is repeated after a rest period determined by the discovery of haematological parameters until complete remission is achieved.

ii). Maintenance (for 24 months)

. Cytosine Arabinoside - 100mg/m^2 (max. 100mg) monthly subcutaneously.

. 6 - Mercaptopurine - 100mg/m2 or 6-Thioguanine 80mg/m^2 orally daily for 5 days.

Management of Meningeal Leukaemia

Depends upon whether there is meningeal involvement at the time of diagnosis.

a) Treatment if there is involvement at the time of diagnosis:

- Intrathecal methotraxate - 10mg/m^2 (max 12mg) daily for 5 doses.
- Rest for 2 days
- Intrathecal cytosine arabinoside - 100mg/m^2 (max. 100mg) daily for 5 days.
- Repeat lumbar puncture to assess the response.

b) CNS Prophylaxis:

- If there is no involvement at the time of diagnosis and when there is complete haematological remission at the beginning of maintenance therapy.

. Intra-thecal methotraxate 100mg/m^2 five doses in three weeks (or cytosine arabinoside 100mg/m^2).

. Cranial radiation, 2500 rads in three weeks after intra-thecal drugs.