TITLE

ENDOCRINE FUNCTION IN MALNOURISHED) CHILDREN ADMITTED AT KENYATTA NATIONAL HOSPITAL.

BY

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DECLARATION

I certify that this dissertation is my original work and has not been presented to any other University for the purpose of obtaining a degree.

Signed .....

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SUMMARY

59 children admitted with various degrees of protein energy malnutrition and 25 controls who were matched for age and sex were examined. Serum growth hormon cortisol and insulin levels were assayed by radioimmunoass Significant elevation of growth hormone and cortisol were observed in the malnourished patients as compared to the normal controls. Significant reduction in insulin levels were also observed in the patients. These changes suggest an endocrinal adaptation in malnourished children for maintainance of various physiological functions.

INTRODUCTION

Malnutrition is a syndrome caused by inadequate or excessive intake of various nutrients. By and large in developing countries the main forms of malnutrition encountered are due to inadequate intake and are characterised by various clinical entities.

In 1971 it was estimated that 500 million people were affected by malnutrition in less developed countries (1). In Kenya 20% of the population is under five years of age (2). It is estimated that 20 - 30% of the under five population suffer from mild to moderate malnutrition. 2- 5% are severely malnourished (3).

Protein energy malnutrition (PEM) is characterised by the clinical syndromes of Kwashiorkor (due to deficiency of proteins mainly) and marasmus (due to deficiency of both calories and proteins).

Although the main deficiency is in protein and energy food stuffs other deficiencies such as vitamin deficiency occur and contribute to the complex clinical presentation as seen in Kwashiorkor.

Various hormones such as growth hormone, insulin, thyroxine and androgens are necessary for normal growth of an individual.

Growth hormone promotes protein synthesis and in conjunction with insulin enhances amino acid uptake by cells (4). It is released in association with excercise, at onset of deep sleep or in response to falling blood sugars one to two hours after meals.

Insulin release is triggered by hyperglycaemia or infusion of leucine (5). It then stimulates entry of glucose into adipose, and muscle thus lowering blood sugar. It also stimulates amino acid uptake by cells. It antagonises the action of growth hormone and cortisol.

Serum cortisol levels are controlled by an inherent circardian ryhthm. Its synthesis and release is influenced by adrenal corticotrophin hormone (A.C.T.H.) secreted by anterior pituitary. Stress whether physical or mental is another important factor which can overide the first two mechanisms (6,7).

One then would expect an endocrinal adaptation or adjustment to help cope up with the stress of PEM. Growth retardation in itself may be a remarkable adaptation to the stress of PEM (8).

Studies done elsewhere have shown that growth hormone levels and cortisol are elevated in both Kwashiorkor and marasmic children (5, 9, 10). This elevation of growth hormone due to malnutrition does not appear to be limited to children only.

Vincet and Howard studying two ladies with anorexia nervosa found that the fasting growth hormone levels were elevated to very high levels and varied slightly with induced hypoglycaemia (11). These elevated levels of growth hormone were shown to be associated with low serum albumin (5, 9, 12).

The elevated cortisol contributes to some of the observed clinical features of Kwashiorkor e.g. moon face, abnormal glucose tolerance test and tendency to oedema. These high levels may lead to or may be associated with the observed decrease in cell mediated immunity.

The low insulin levels in children are thought to be due to hypoglycaemia secondary to decreased food intake (13). The decrease in insulin level is thought to be the main regulator of release of energy metabolites from endogenous sources. There is then increased mobilisation of skeleton muscle protein due to increased cortisol with release of amino acids which are used in gluconeogenesis. Some of the amino acids are also used in synthesis of proteins. Increased growth hormone while helping in nitrogen retention brings about lipolysis with release of free fatty acids. This seems to be further evidence of endocrinal adaptation in malnourished children to try and maintain various physiological functions.

On review of literature no endocrine function studies in malnourished children have been done in Kenya.

It is lack of data which stimulated the authcr to undertake this study.

OBJECTIVE

To detetmine the serum growth hormone, insulin and cortisol levels in children admitted with severe malnutrition (Kwashiorkor, marasmus and marasmic-Kwashiorkor) at Kenyatta National Hospital.

MATERIALS AND METHODS

The study was conducted over a period of six months from March to August 1985. During that period a total of 327 patients were admitted to Kenyatta National Hospital with varying degree of malnutrition. Out of this 59 (16.5%) were recruited into the study.

Patients to be entered into the study were recruited on the evening of their admission. All patients admitted due to malnutrition on Sunday, Tuesday and Thursday were examined by the author. Patients were placed into various groups of malnutrition using the wellcome classification (14). Those patients with overt signs of infection and obesity were excluded from the study. Three groups of patients were recruited. Those with kwashiorkor, marasmus and marasmic-kwashiorkor. Details on the patients age, sex, weight, presence of oedema, muscle wasting, and growth failure were recorded as per attached data sheet (appendix I).

Weighing

The weight of patients was taken on admission using Taledo weighing machine model 1361, which was calibrated to zero mark every morning as per instructions from the manufacturers.

The following morning a sample of venous blood (4 millilitres) was taken by venepuncture from cubital or external jugular vein. One and one-half millilitres was put in a flouride bottle for blood sugar estimation and the other two and one-half millilitres were put in a plain bottle. The serum from the second sample was separated within one hour of specimen collection and stored at minus (-) 4 degrees centrigrade.

All samples of blood were taken between 8 - 9a.m the following morning after patients had been recruited. All patients had had break-fast one and a half to two hours in form of porridge before sample of blood was taken.

Controls

Controls were age and sex matched from children attending hospital for minor surgical procedures such as herniorrhaphy and hypospadias. These children did not have any nutritional problem. Only those who spent the night in the hospital were considered. This was to help minimise or make uniform the stress between the patients and the controls.

A sample of blood was taken between 8 - 9a.m. the following morning and was handled in the same way as the one from patients.

Ethical Consideration

A written consent was obtained from the parents or guardian of both controls and subjects before they were entered in the study as required by the ethical committee of Kenyatta National Hospital.

Laboratory Methods

Assay of serum insulin, growth hormone and cortisol were done by Radioimmuno-assay (RIA) using kits from the diagnostic products corporation. This is a saturation assay technique (15). It relies on I^{131} labelled hormone which competes with the particular hormone to be assayed in the patients sample for sites on hormone specific antibody immobilised to the wall of a polypropylene tube.

After incubation, isolation of the antibody bound fraction was achieved simply by decanting the supernatant. The tube wasthen counted in a gamma counter, the count being inversely related to the amount of hormone being assayed in the patients' sample. The quantity of hormone in the sample was then determined by comparing the counts to a standard curve. The standard curve was obtained by plotting standard samples of known hormone level concentration provided by the manufacturerson a logarithimic graph. The basic principle for assay to different hormones was as outlined above with only minor variations on duration of incubation.

Serum albumin

Serum albumin assay was done using automated method based on dye binding with bromocresal green which has the advantage of ease of reproducability and requires only a small volume of patients serum (0.2 mls) (16) . This analysis was done after all the specimens had been collected.

Blood Sugar

Blood sugar assay was done using the glucose oxidase method (17, 18). The only modification was use of gualcum instead of O-tolidine. The latter has been shown to have carcinogenic effect.

RESULTS

A total of 59 patients and 25 controls were examined. 26 had Kwashiorkor, 22 had marasmic-Kwashiorkor and 11 had marasmus. Below are tables and figures of results.

BLE I: SERUM GROWTH HORMONE CORTISOL AND INSULIN LEVELS IN PATIENTS AND CONTROLS.

HORMONE ASSAYED	PATIENTS N = 59		CONTROLS N = 25
GROWTH HORMONE ng.ml	$\bar{x}$	18.47	1.65
	SD	8.3	1.2
CORTISOL µg/dl	$\bar{x}$	32.27	16.58
	SD	17.6	10.0
INSULIN µU.ml	$\bar{x}$	1.22	9.64
	SD	1.7	2.22

GROWTH HORMONE

Growth hormone levels were significantly elevated in the patients group as compared to the controls ($P<0.001$).

CORTISOL

Cortisol levels were also significantly elevated in the patients as compared to the controls ($P<0.001$).

INSULIN

Controls had on a verage higher insulin levels as compared to the patients $P = 3$

BLE II: SERUM GROWTH HORMONE CORTISOL AND INSULIN LEVELS IN VARIOUS PATIENTS GROUPS AND CONTROLS.

		KWASHIORKOR N = 26	MARASMIC KWASHIORKOR N = 22	MARASMUS N = 11	CONTROLS N = 25
GROWTH HORMONE ng/ml	$\bar{x}$	18.9	18.2	16.5	1.65
	SD	8.4	8.5	8.3	1.2
CORTISOL µg/dl	$\bar{x}$	31.6	36.5	31.5	16.58
	SD	17.2	17.7	19.7	10.0
INSULIN µU/ml	$\bar{x}$	1.62	1.05	0.9	9.64
	SD	2.79	1.29	1.03	2.22

There was no significant statistical difference between the different patient groups tested against each other.

Growth hormone $x_2^2 = .32$

Cortisol $x_2^2 = .22$

Insulin $P < .50$

TABLE III: BLOOD SUGAR LEVELS IN THE PATIENTS AND CONTROLS

	PATIENTS n = 56	CONTROLS n = 25
BLOOD SUGAR mmol/l	$\bar{x}$ = 5.57 SD = 2.15	$\bar{x}$ = 4.58 SD = 1.78

Patients had a higher mean than the controls.

This difference was statistically significant.

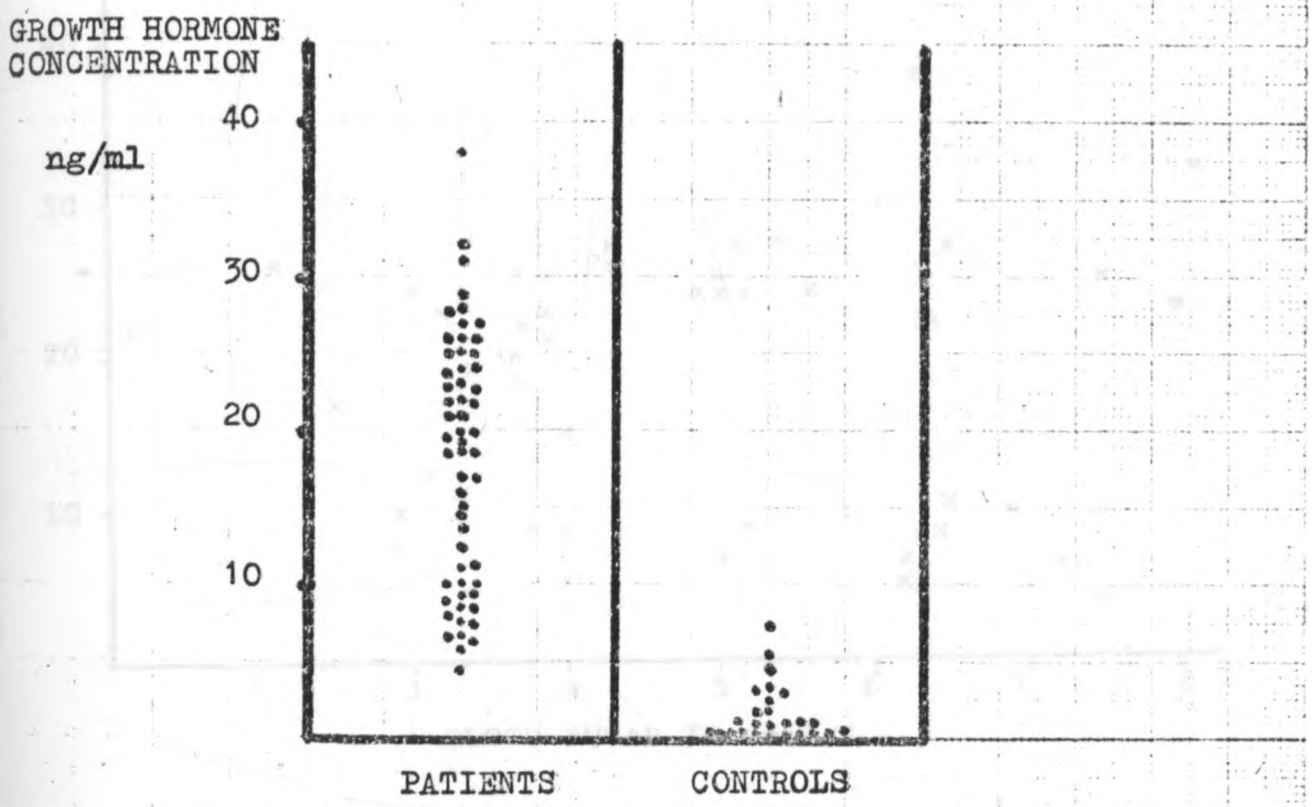
$P < 0.05$. These were random blood sugars (not fasting).

TABLE VI: SERUM ALBUMIN IN THE PATIENTS AND CONTROLS.

	PATIENTS n = 56	CONTROLS n = 25
Serum Albumin gm/litre	$\bar{x}$ = 20.6 SD = 7.42	42.0 4.49

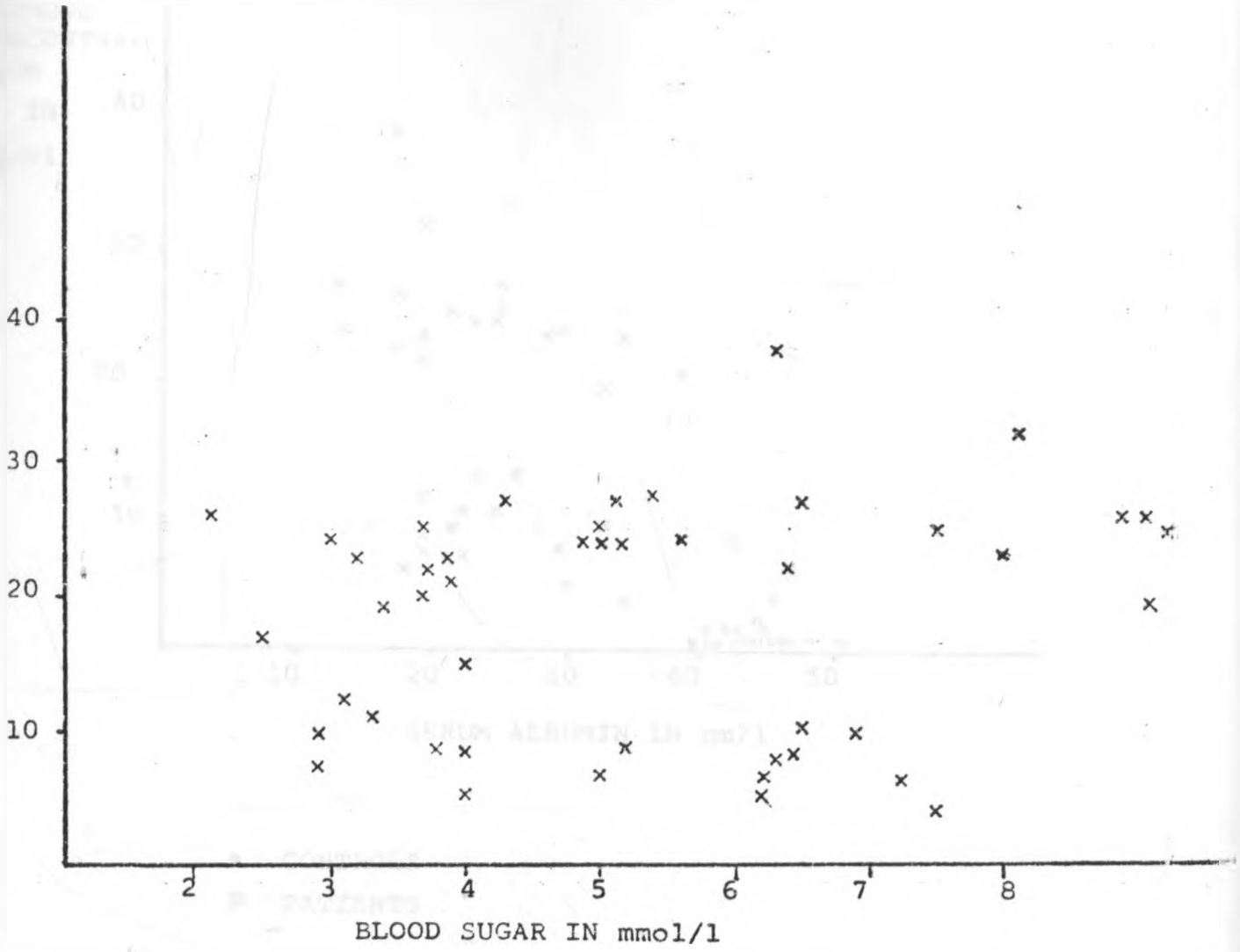
Patients had lower serum albumin levels as compared to the controls ($P < 0.001$).

FIGRE I: SERUM GROWTH HORMONE LEVELS IN THE PATIENTS AND CONTROLS



Growth hormone is significantly elevated in patients as compared to the controls $P < 0.001$

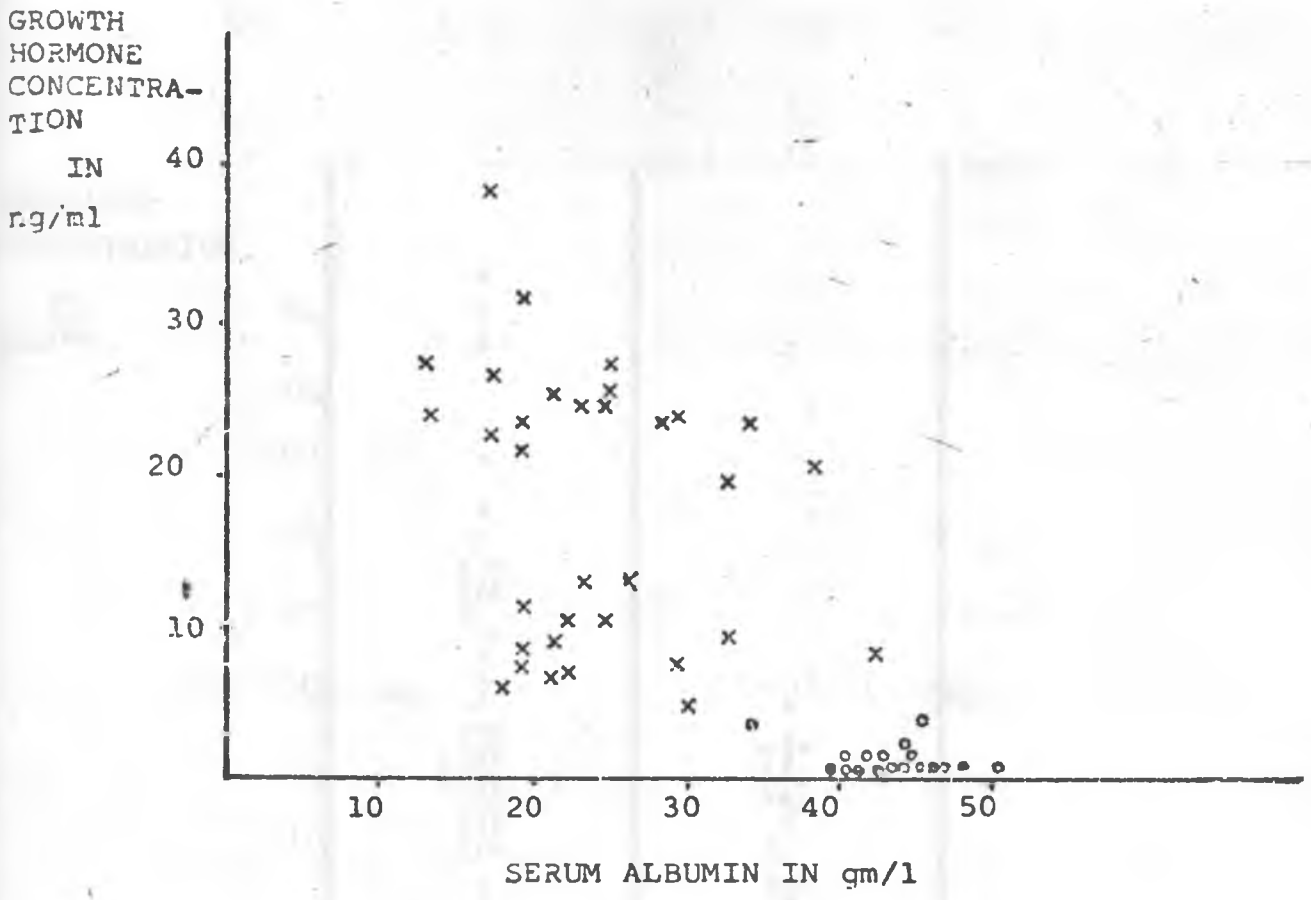
FIGUPE II: CORRELATION SCATTERGRAM OF SERUM GROWTH HORMONE AND BLOOD SUGARS.



No correlation was observed between growth hormone levels and blood sugars

$t_{57} = 0.34, \quad P < 0.5$

FIGURE III: CORRELATION SCATTERGRAM OF SERUM GROWTH HORMONE AND SERUM ALBUMIN.

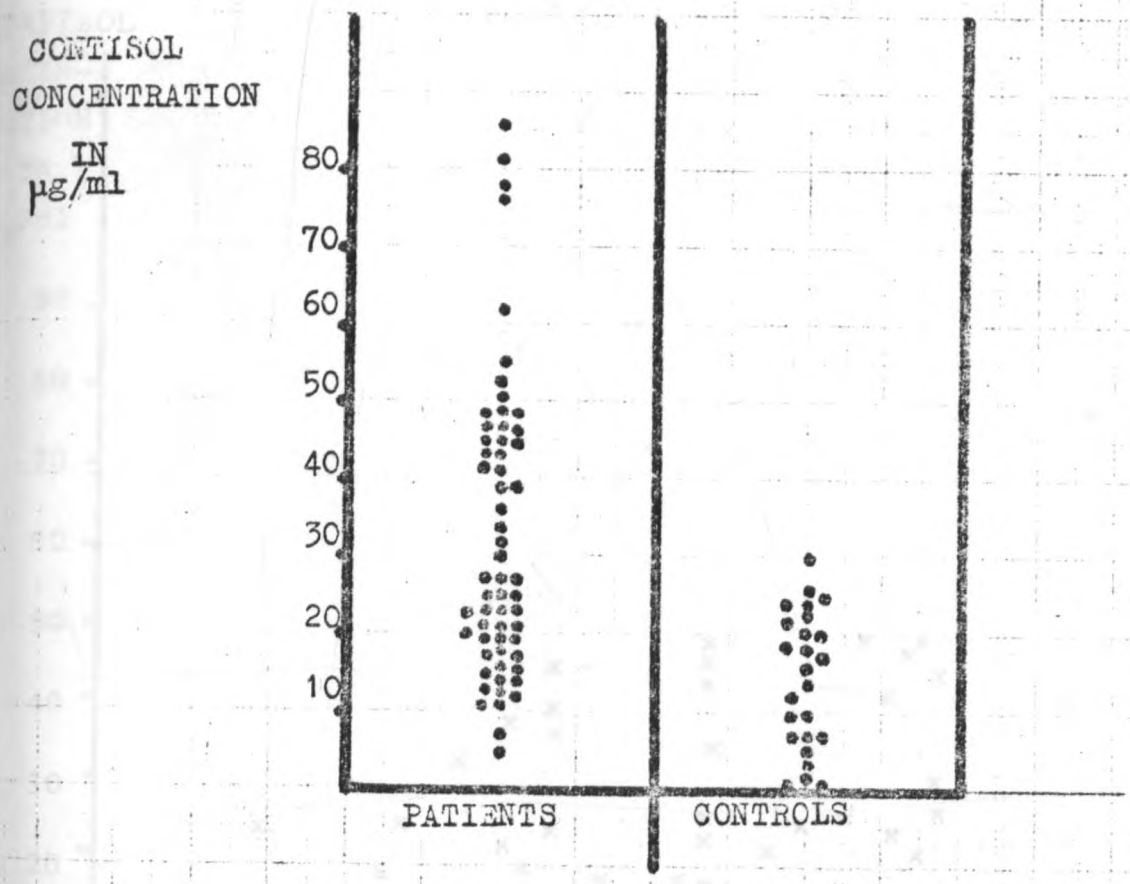


• CONTROLS

✱ PATIENTS

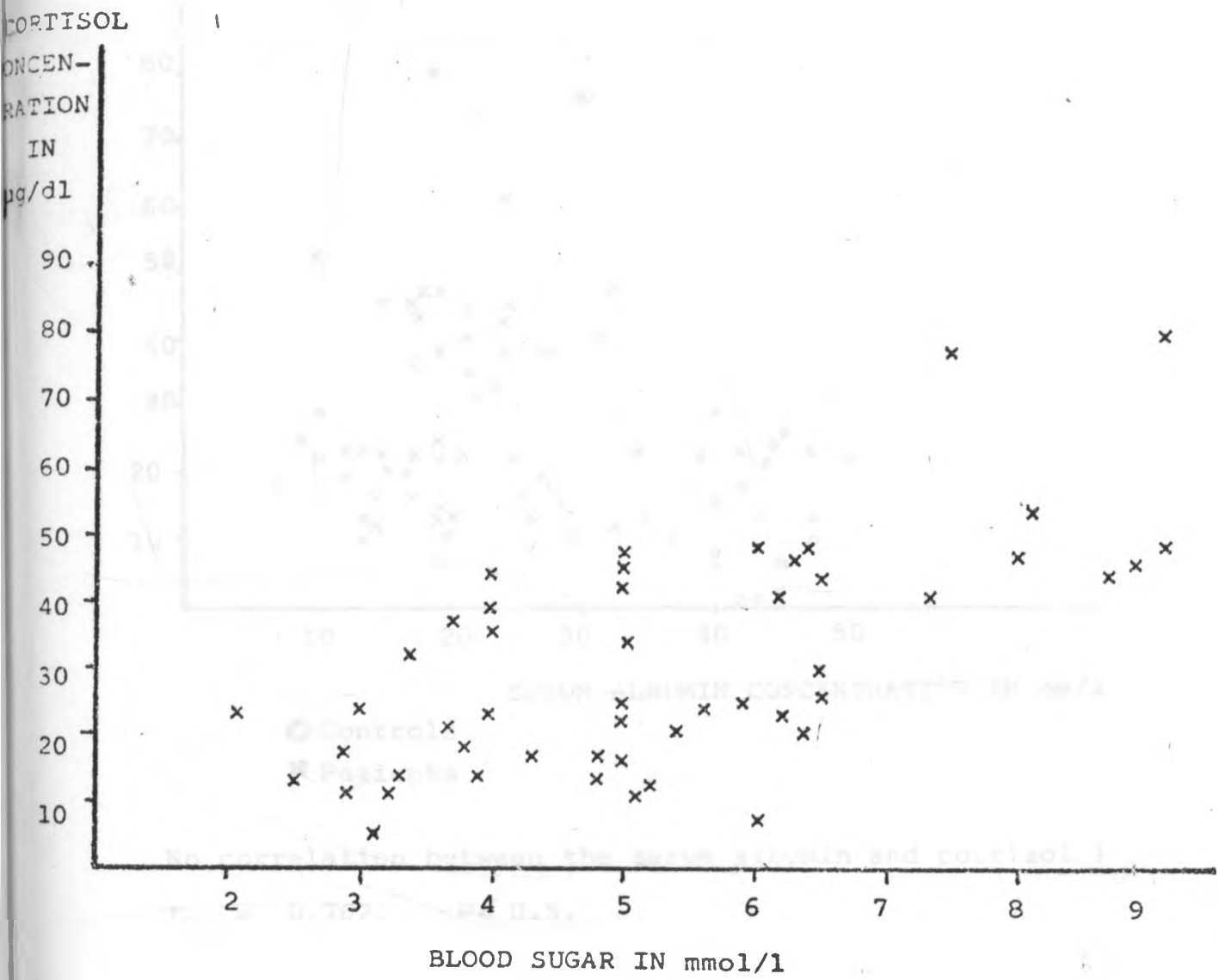
There was a negative correlation between the serum albumin and growth hormone levels in the patient group. ($r = -0.36$).

FIGURE IV: SERUM CORTISOL LEVELS IN PATIENTS AND CONTROLS



Cortisol levels were significatly elevated in the patients as compared to the controls $P < 0.001$

FIG V: CORRELATION SCATTERGRAM OF CORTISOL AND BLOOD SUGAR.

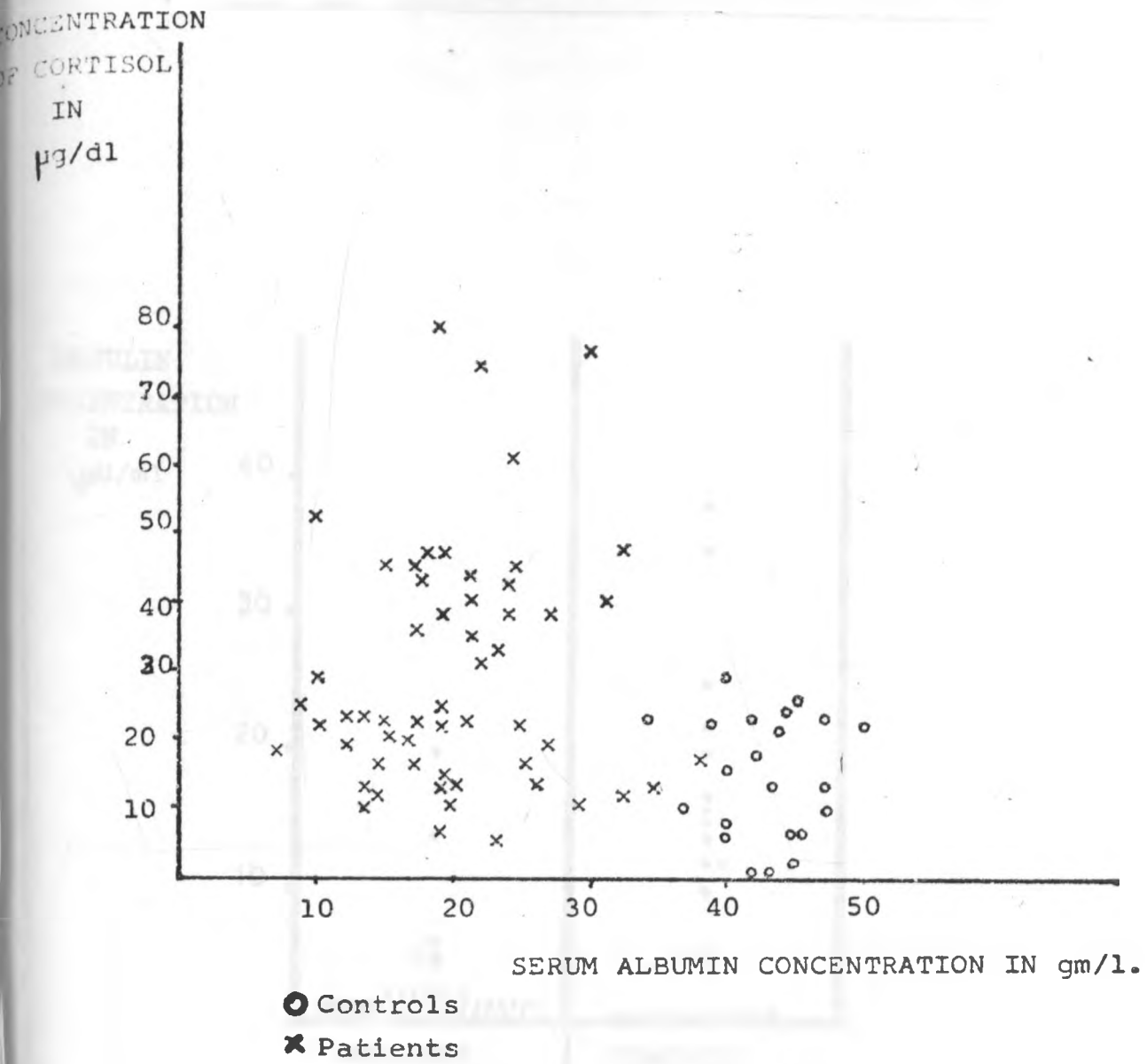


A positive correlation between the levels of cortisol and blood sugars was observed r= 0.62

Cortisol = 5.26 (Blood sugar + 2.21)

Blood Sugar = 0.071 (Cortisol + 3.31).

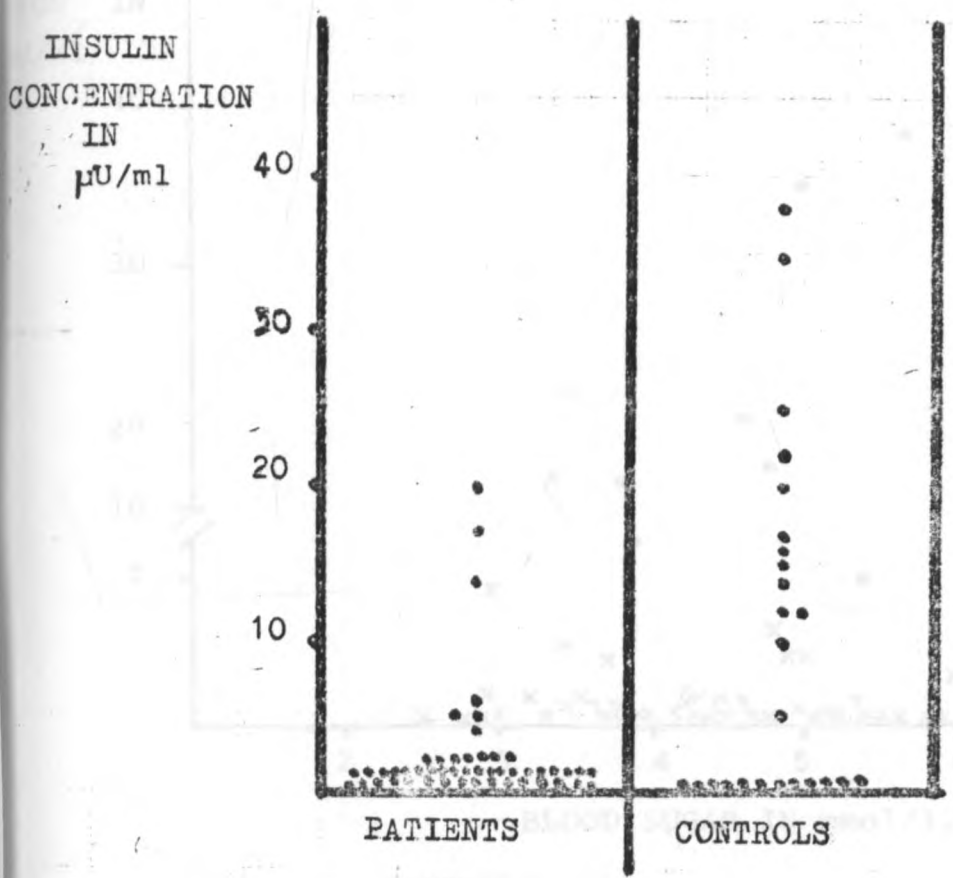
FIGURE VI: CORRELATION SCATTERGRAM OF CORTISOL AND SERUM ALBUMIN.



No correlation between the serum albumin and cortisol levels.

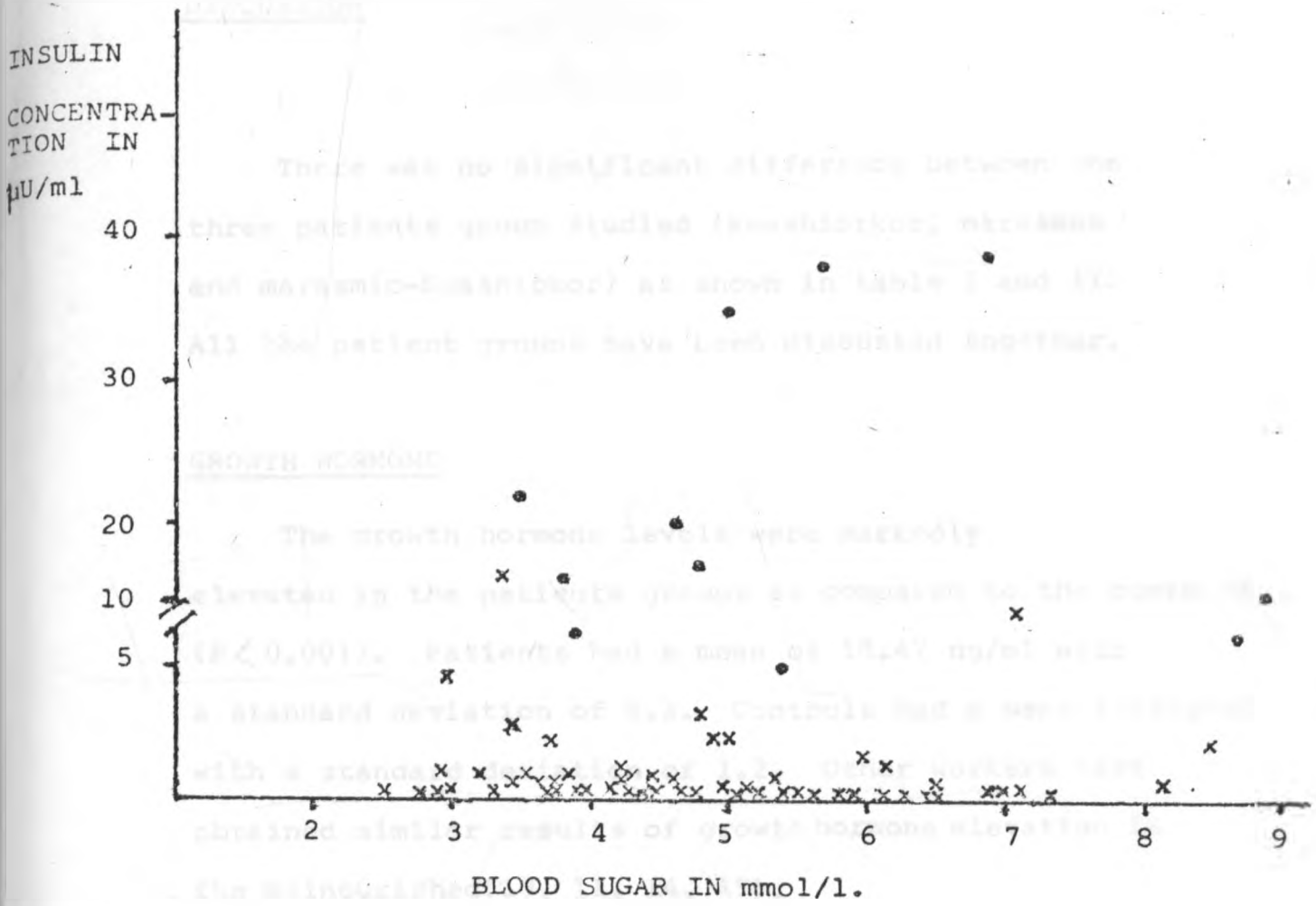
$t_{57} = 0.762, \quad P < 0.5.$

FIGURE VII: SERUM INSULIN LEVELS IN PATIENTS AND CONTROLS



The levels of insulin were much higher in the controls as compared to the patients P = 3

FIGURE VIII: CORRELATION SCATTERGRAM OF INSULIN AND BLOOD SUGARS.



The patients had lower insulin levels even when the blood sugars were within the same range as non-malnourished controls. Low insulin levels could account for the higher blood sugar levels.

DISCUSSION

There was no significant difference between the three patients group studied (Kwashiorkor, marasmus and marasmic-Kwashiokor) as shown in table I and II. All the patient groups have been discussed together.

GROWTH HORMONE

The growth hormone levels were markedly elevated in the patients groups as compared to the controls ($P < 0.001$). Patients had a mean of 18.47 ng/ml with a standard deviation of 8.3. Controls had a mean 1.65ng/ml with a standard deviation of 1.2. Other workers have obtained similar results of growth hormone elevation in the malnourished(10, 11, 14, 19).

Several explanations have been put forward for the marked elevation the growth hormone. Pimstone et al demonstrated high elevation of growth homone in children with Kwashiokor and marasmus(13). These levels fell to normal after two to three weeks of feeding. The levels started falling on 3rd day of protein diet but failed to drop if only a diet of carbohydrate

was given. He also demonstrated a negative correlation between the levels of growth hormone and serum albumin. This negative correlation was also demonstrated in the present study as shown in figure three (fig. III). Becker et al also demonstrated a negative correlation between the growth hormone levels and serum albumin (20). He infused albumin intravenously but this did not bring down the level of growth hormone. Oral milk brought down the levels of growth hormone inspite of little change in serum albumin. He concluded that the negative correlation of growth hormone and serum albumin was a parallel consequence of severe PEM and the important thing in elevation of growth hormone was serum amino acids.

Saunder et al studying the pattern of free amino acids in PEM demonstrated low levels especially the essential amino acids, leucine, isoleucine and valine (21). He demonstrated no correlation of low levels of amino acids with clinical severity or with serum albumin levels. There was a striking rise in plasma free amino acids within twenty four hours of commencement of protein feeding.

Pimstone also demonstrated elevated growth hormone levels in a 55 years old man who had gastrectomy and malabsorption.

Figure II shows the correlation between the growth hormone levels and blood sugar. There was no correlation between the two variables. Other workers have not demonstrated any correlation between the two(11, 12). Although there was statistical difference in the levels of blood sugars between the patients and the controls, it appears that the increase in the growth hormone level is not directly related to maintance of blood sugar. Some workers have found very high levels of growth hormone to be associated with normal or even low blood sugar levels (19).

Somatomedin which mediates the effect of growth hormone on skeletal growth has been observed to be low (22, 23). One of its sites of release is the liver (24, 25). An inverse relationship between somatomedin and growth hormone has been observed. High growth hormone levels and low somatomedin levels may be due to impaired somatomedin synthesis in the liver. The low somatomedin may then lead to elevation of growth hormone through negative feed back on the pituitary.

On follow up of patients, Solmon et al (22) observed a gradual rise of somatomedin as growth hormone fell to lower levels in malnourished. However Grant et al found no correlation between growth hormone and somatomedin. They observed that since somatomedin is a peptide, low levels may be a reflection of an abnormality of protein synthesis by the liver. This would be a part of general breakdown in homeostatic mechanism in the malnourished.

If low somatomedin is adaptive, it would be advantageous in diverting the scarce resources from long term needs of growth to more urgent needs. As to which process is taking place (breakdown or adaptive) is difficult for one to conclude at this stage.

Low amino acids may be concerned with the feed back stimulation of growth hormone secretion. Administration of amino acids has been shown to lower the levels of growth hormone (27). The growth hormone may then be geared towards increasing efficiency of utilisation of amino acids which are sparingly available.

CORTISOL

The cortisol levels in the three patients groups were markedly elevated ($P<0.001$). There was no statistically significant differences between the three groups ($x^2_2 = 0.22$). The means were Kwashiorkor 31.6 µg/dl, marasmus 31.5 µg/dl, marasmic-Kwashiorkor 36.5 ug/dl, with an average mean of 32.27 µg/dl. All the patients groups have been put together for the discussion.

Various workers have also demonstrated elevated cortisol levels in malnourished children(5, 13, 28, 29). Munro in his work suggested that the level of adrenal cortisol activity plays a crucial role in adaptation of the organism to stress of PEM (8, 30, 31). A dietary survey in India revealed no difference in those who developed Kwashiorkor and those who became marasmic (32). The children who develop marasmus are said to be able to adapt to the stress of PEM. While those who develop Kwashiorkor have been unable to adapt. The initial response in PEM is to increase the level of glucocorticoids which leads to mobilisation of amino acids from muscles.

This is accompanied by severe wasting as seen in marasmic children. The available amino acids are utilised in synthesis of proteins in the liver e.g. lipoproteins which are necessary for transport of triglycerides from the liver to adispose tissue (33). It is this kind of adaptation which if it fails leads to development of Kwashiorkor, with impaired hepatic function and fatty liver. Jaya did a study with monkeys who were fed on low protein diet. One group was injected with cortisol daily while the other one was not. He demonstrated that the cortisol protected the monkeys from developing a fatty liver or overt signs of Kwashiorkor (34). He also demonstrated higher cortisol levels in marasmic children than in Kwashiorkor. Srikantia et al also demonstrated higher cortisol levels in marasmic children 31.5 $\pm$ 5.34 ug/dl as compared to Kwashiorkor patients 24.9 $\pm$ 1.95 (35).

This was not demonstrated in the present study. One possibility is that by the time patients with malnutrition are admitted to hospital, other endocrinal changes have taken place due to infection or underfeeding which may cause marked rise in cortisol levels (5, 28).

Fig V shows the correlation between the of cortisol levels and blood sugars. There was a positive correlation between the two variables. The correlation coefficient was $\sqrt{}$ 0.62,(P 0.01). The correlation was such that one can predict the blood sugar levels given the cortisol levels of the patient:or predict the cortisol levels given the blood sugar levels: By.

Blood sugar = 0.074 x (cortisol + 3.31).

Cortisol levels = 5.26 x (blood sugar + 2.21).

Whitehead and **Alleyne** found high cortisol levels to be associated with low blood sugars (28). In that study the blood sample was taken the first thing in the morning (fasting). In the present study all patients had had break-fast 2 - 3 hours before the blood was taken (as explained in the materials and methods).

On the other-hand normal or elevated blood sugars associated with higher cortisol levels could be a result of increased gluconeogenesis from amino acids mobilised from muscle by effect of cortisol

Fig VI shows the correlation between the levels of cortisol and serum albumin. There was no correlation between the two variables - correlation coefficient $\sqrt{}$ 0.25.

INSULIN

The insulin levels in patients with PEM were found to be decreased as compared with the controls. The mean in the patients was 1.62 μU/ml, standard deviation of 2.79 as compared to the controls who had a mean of 9.64 μU/ml, standard deviation of 2.22. This difference was statistically significant (P = 3). Other workers have found low insulin levels in malnourished (5, 13, 28, 36, 37).

Low levels of insulin observed in malnourished children would allow the growth hormone and cortisol to act without any antagonism. This may lead to hyperglycaemia due to increased gluconeogenesis, and glycogenolysis (4, 5, 6). In the present study, the patients had a higher mean blood sugar of 5.57 mmol/dl, with a standard deviation of 2.15, as compared to the controls who had a mean 4.58 mmol/dl and standard deviation of 1.78. These differences were statistically significant. The higher mean in the patients could be due to the low levels of insulin and high levels of growth hormone and cortisol. Becker et al observed impaired glucose tolerance test (38). Other workers have also reported impaired glucose tolerance test (37, 38, 39).

Some workers have demonstrated impaired response to glucose lead several years after recovery (28,37). This would suggest that some permanent β - cell damage may result from malnutrition. These could be as a result of juvenile tropical pancreatitis syndrome. This syndrome has been described in those areas of tropical countries where diet consists mainly of carbohydrate and there is repeated infection causing gastroenteritis and amorexia. One of the complication that results is pancreatitis (40, 41, 42).

Persistent low levels of insulin would mean impaired utilisation of glucose. As to whether the low level of insulin is an adaptation to the stressful situation of underfeeding or is due to pancreatitis is difficult to conclude from the available literature.

CONCLUSIONS

This study has demonstrated the following changes in malnourished children.

1. The growth hormone levels in malnourished children are significantly elevated, but no significant differences was observed between Kwashiorkor, marasmic-Kwashiorkor, and marasmus.

2. The cortisol levels are significantly elevated in malnourished children, but there are no significant differences between Kwashiorkor, marasmic-Kwashiorkor, and marasmic patients was observed.

3. Insulin level in the malnourished children were significantly lower in comparison to the non-malnourished controls.

4. There was no hypoglycaemia observed in the patients (though a common problem in fasting state).

5. The malnourished children had significantly lower levels of serum albumin as compared to the non-malnourished controls.

RECOMMENDATION

The following studies would be useful as a follow up of the present study.

1. A study to find out the correlation between growth hormone and serum amino acid levels.

2. A study of somatomedin levels in malnourished children in relation to growth hormone levels.

3. A follow up study of malnourished children to find out whether low insulin levels persists after recovery from PEM. A follow up study to find out whether glucose intolerance occurs later on in life would be advisable.

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APPENDIX I

DATA SHEET STUDY NO.

NAME OF PATIENT IN PATIENT No.

Age in months Sex

Weight on Admission

Presence of Oedema Yes ..... No.....

Mental Changes Yes ..... No.....

Growth failure Yes ..... No.....

Muscle Wasting Yes ..... No.....

Percentage of expected weight %
. (Calculated).

Category of Malnutrition

(i) Kwashiorkor -

(ii) Marasmic-Kwashiorkor -

(iii) Marasmus -

LABORATORY RESULTS

Blood Sugar - mmol/dl

Serum Albumin - Gm/l.

Growth Hormone - ng/ml

Cortisol - µg/d

Insulin - µU/ml.