DISCUSSION
Unfortunately in most of the studies protein calorie malnutrition has been treated as a group and in very few studies kwashiorkor has been differentially investigated from marasmus. However, we think it is important to differentiate between the two syndromes where investigations of carbohydrate metabolism are concerned. Classical kwashiorkor, i.e. those with growth failure, edema, hepatomegaly, dermatoses, mental apathy has never been shown to occur without a predominantly starchy diet. Such starch diet naturally would have its concomitant metabolic features like those on glycogen synthesis, mobilization of fat and endogenous nitrogen and sugar utilization. Of course, the overall pattern would depend on the activation and functioning of the enzymes, which would be dependent on the amount of protein availability from the diet.

Classical kwashiorkor should be differentiated from marasmic kwashiorkor which is nothing but marasmus on the top of which there is edema and hypoalbuminemia. These cases are really cases of marasmus but probably due to some additional stress there is hypoalbuminemia which leads to edema. So, any case of protein calorie malnutrition in children which shows edema should not be strictly classified as kwashiorkor where some special metabolic features like carbohydrate metabolism.
are being studied. In contradistinction to kwashiorkor, marasmus is associated with inadequate dietary intake as a whole. In experimental animals too, diet low in calories and protein produces marasmus but in order to produce edema and fatty liver, we have to force feed the animal on a starchy diet.

The literature is replete with references of the state of hypoglycemia in protein calorie undernutrition in children. Some workers report normal blood sugar (Bowie, 1964; Rao, 1965), while others report hypoglycemia (Hadden and Beif, 1967; Kerpel-Fronius and Kaiser, 1967; Aballi, 1950; Kahn & Wayburne, 1960). Two things must be considered in this regard - 1) the severity of the undernutrition and 2) the character of the undernutrition. The more severe and prolonged the undernutrition is, the more chances there would be of hypoglycemia. This is true of acute starvation and probably also true of chronic undernutrition. When dogs were acutely starved for 30 days, the blood sugar content progressively fell from 116 mg% to 91 mg% (Otto, 1885). However species variation exists; in the majority of the animals there was an initial decline of blood sugar value followed by a later increase (Shope, 1927; HerschyiOrr, 1928).

In a normal young woman who went without food for 5 days, it was shown that the blood sugar decreased from 110 mg%
to 37 mg% on the 4th day and then increased to 68 mg% on the 5th day (Shope 1927). The initial decrease was probably due to gradual exhaustion of glycogen reserve, while the system was being adjusted to the fasting. The later increase was a manifestation of adjustment, mainly by gluconeogenesis.

Chronic malnutrition was, however, a matter between the adjustment of the body and the inadequate diet. In adult persons, exposed to chronic undernutrition like the German prisoners of war, there are conflicting reports about the glycemic condition. In world war I, Knack and Neumann (1917) found blood sugar level to be normal in patients with hunger edema. So also did Leyton (1945) in world war II. However, a number of French, Belgian and Polish investigators reported hypoglycemia (Gouenelle and Marche, 1946; Bastenie, 1947; Fliederbaum et al, 1946).

The hypoglycemia at times was severe enough to produce symptoms and they attributed to hypoglycemia the immediate cause of death. In the Burma evacuees coming to India during world war II, the nutritional status of the people was in extremely wretched condition and a large number of the people suffered from severe cachexia and what was then called hunger edema. Bose et al (1947) reported hypoglycemia in such individuals sometimes the blood sugar level went down to very low levels (as low
as 17 or 16 mg\% but still the clinical symptoms of hypoglycemia was very rarely found. Mazumder and Mukherjee (1951) also reported very low blood sugar in some adult patients suffering from Nutritional Edema during famine. Such patients however had some signs of hypoglycemia.

The children, perhaps, adapt to semistarvation andos to hypoglycemia in a different way than adults. Hypoglycemia is not an uncommon finding in the newborn, especially in the premature babies. But seldom do they exhibit symptoms of hypoglycemia. Chaudhuri (1948) found the blood sugar level of children suffering from malnutrition to lie between 60 and 80 mg\%; Kerpel-Fronius (1967) found hypoglycemia to be in rough correspondence with the degree of muscle wasting. He as well as Del Pino (1955) and Aballi (1950) found extreme hypoglycemia in some children with malnutrition and they attributed the deaths in some of these cases to the hypoglycemia. Waterlow, Cravioto and Stephen (1960) thought that it was unlikely that the mortality could be due to hypoglycemia since intravenous administration of glucose did not reduce the mortality. The general opinion, however, is that children suffering from kwashiorkor do not have hypoglycemia. In most of the latter studies, however, kwashiorkor was not distinguished from marasmus and where it was done, any child suffering from general
malnutrition and edema was classified as kwashiorkor. In the present series of 202 children, 67 suffered from classical kwashiorkor, 85 from marasmus and 50 from nutritional edema (according to the clinical classification of Mukherjee, 1967). The fasting blood sugar content in kwashiorkor, on admission of the patients, was lower than that obtained before discharge. The difference was statistically significant (p < 0.01). In marasmus it was not so. Furthermore, in nutritional edema, i.e., marasmic kwashiorkor there was virtually no difference in the blood sugar contents on admission and before discharge. If, therefore, any case of protein-calorie undernutrition in children manifesting edema be classified as kwashiorkor, there is a chance that the incidence of hypoglycemia would be missed and would not appear significant. The question, therefore, arises, why is hypoglycemia present in a significant number of cases suffering from kwashiorkor and it is virtually absent in nutritional edema; Both kinds of children were seriously sick, at least as far as the total mortality is concerned; i.e. taken as a group, there was a mortality of around 30% in both groups. Whereas in nutritional edema, no case of hypoglycemia was seen among 20 children, about a quarter of the children suffering from kwashiorkor had hypoglycemia. The mortality in the hypoglycemic was seven times that in the
normo-glycemic group.

One difference between kwashiorkor and nutritional edema is the presence of a high free fatty acid content of the plasma in kwashiorkor in contrast to a low plasma free fatty acid level in nutritional edema. In nutritional edema there is virtually total absence of subcutaneous fat and other storage fat. There is no fat to mobilize. Whereas in kwashiorkor there is some storage fat to mobilize (Ganguly, Chatterjee & Mukherjee, 1972). Is it possible that oxidation of fatty acids in states of protein depletion produces some untoward effects on glycogen breakdown? We do not know.
Approximately 1/5th of the children (13%, 32 out of 172), suffering from severe kwashiorkor had hypoglycemia (i.e., in these children the blood sugar was less than 50 mg%). In five of these children the blood sugar was less 25 mg%; three of these children died; two survived. Of the other 25 hypoglycemic children 13 died and 7 survived. The overall mortality in the hypoglycemia group was, therefore, 70%. In the normoglycemic group of 140 children, 32 died and 108 survived. The mortality was 22%. The mortality in the hypoglycemic group was approximately three times that of the normoglycemic group. The question, therefore, is pertinent whether hypoglycemia was the cause of increased mortality in the hypoglycemic group. The mortality and the degree of hypoglycemia was not linearly correlated for, among the hypoglycemias, the rate of mortality was the same whether the blood sugar was below 25 mg% or between 25 and 50 mg%.

In general, the hypoglycemias were more seriously ill than the normoglycemias. They had more severe diarrhoea, intense anorexia, more loss of body weight and mental changes than the normoglycemias. Their tissues contained less protein, more water, and less enzymes, as compared to the normoglycemias, as will be shown later. They exhibited more metabolic abnormalities, such as decreased utilization of glucose and free fatty acids. Their response to treatment was poorer. So, taking
all these facts together it can be said that hypoglycemia was one of the serious manifestations of metabolic derangements in this group and might have contributed to the increased mortality in this group but so could the other manifestations in this group.

Hypoglycemia may not be singled out as the sole cause of mortality in this group. Among the 32 hypoglycemics, only five exhibited symptoms of hypoglycemia i.e., collapse, semiconsciousness, pallor and perspiration. So, the majority of the children had adjusted to the low blood sugar content. Such hypoglycemia is in line with the neonatal hypoglycemia found especially in the premature babies; it is possible, therefore, that hypoglycemia in kwashiorkor may be considered to play some role, although not the only contributing factor, towards the mortality of such children.
ORAL GLUCOSE TOLERANCE:

The response of children in the age period of 1 to 4 years to oral administration of glucose depends on -

a) The dose of sugar  
b) The previous diet of the child  
c) The nature and extent of the carbohydrate reserve  
d) The state of gastrointestinal functions  
e) The renal threshold of sugar  
f) The adequacy of renal functions.

The usual procedure of the test is to administer 1.75 g/m of glucose/Kg of bodyweight, but since many of these children on admission had bodyweights of around 4 Kg, a standard dose of 10 g of glucose was routinely given. However, many of these children gained over 3 Kg in 3 months time, so the repeat dose was calculated on the basis of 1.75 g glucose/Kg of bodyweight.

It has repeatedly been stressed in text books that a preliminary feeding of adequate diet for at least 3 days is necessary before the test is undertaken. But, first of all, let us define the term tolerance. Originally the term was intended to signify the quantity of glucose that can be administered to an individual without producing glycosuria, i.e. the individual tolerated upto that amount of glucose. In normal individuals,
possessing normal renal thresholds, glycosuria occurred only if the blood sugar exceeded the threshold. Therefore, in the course of time, the term tolerance came to be associated with the blood sugar level. In persons, with increased tolerance, amounts of glucose larger than in normals was required to raise the blood sugar; for example in malabsorptive state. In persons with reduced tolerance, amounts of glucose smaller than in normals produced a relatively hyperglycemic state; for example in diabetes mellitus.

Preliminary feeding with normal diet is normally necessary in order to evaluate a subsequent oral or even intravenous glucose tolerance test. This is because, a previous low caloric diet would presumably deplete a part of liver glycogen and hence a subsequent oral glucose tolerance might reduce the tolerance, and produce hyperglycemia. On the contrary a previous high carbohydrate diet would have stimulated the pancreas to secrete insulin, and a subsequent oral glucose tolerance test would result in greater and earlier stimulation of insulin with resultant lowering of the glycogen response. The liver would perhaps, be full of glycogen, so there would be abundant amount of glycogen to draw upon in the post-absorptive phase. Since these variations in the previous diet were found to influence the glycemic response after a test meal of glucose, a standard glucose
tolerance test is usually done after a preliminary feeding of around 350 g of glucose for 3 days prior to the test. However, the above conditions were standardized after having a diagnosis of diabetes mellitus or hyperinsulinoma in mind, and the subject was either an adult or a young adult.

The conditions have not been standardized for infants and children. Under such circumstances, it is, perhaps, preferable to have the children put on his normal diet for the age for 3 days before undertaking the test.

In protein-calorie undernutrition, such a preliminary feeding with normal diet for the age for 3 days would not be either possible or desirable. It would not be possible because most of these children are in such a seriously depleted states that they would not tolerate such a diet at the outset. It would not be desirable because feeding the normal diet even for three days would produce corresponding alterations in the very constituents we were desiring to investigate, namely, the factors dealing with carbohydrate metabolism. Hence, in our experiments, no previous feeding regimen was used.

As noted, the glycemic response depends on the state and nature of liver glycogen. The blood sugar
in the postabsorptive stage is maintained by glycogenolysis and gluconeogenesis. The post absorptive phase in glucose tolerance test, perhaps, occurs after 2 hours, i.e. absorption is completed by 2 hours. The phase of the tolerance curve between 2 hours and after, therefore, is conditioned by glycogenolysis and gluconeogenesis. If the subject undergoing this test would have no glycogen to break down or any available protein to be converted to glucose, this phase of the sugar tolerance would be profoundly affected. The earlier phase of the sugar tolerance curve would also be affected by the state of liver glycogen. If the stores are depleted, more sugar would be channelized to replete the store. If they are full, more will go into other cells like the adipose tissue cells to be converted to lipids. All the processes are enzyme dependent.

The glycemic response in oral glucose tolerance is, of course, dependent on the state of the absorptive function of the intestine. Absorption of glucose from the intestine occurs against a concentration gradient and is an active process (Wilson, 1962). In malabsorptive states like tropical sprue, nontropical sprue, Coeliac disease, severe diarrhoea, absorption of glucose is impaired and the oral glucose tolerance tends to be flat.
Children who died of kwashiorkor the small intestine is thin like paper and the mucosa on the villi are atrophied and oedematous. It is very probable, therefore, that oral glucose tolerance would be affected in kwashiorkor.

In some persons the renal threshold for sugar is decreased and sugar appears in the urine even when the blood sugar level is well below 180 mg%. Such persons are said to suffer from benign glycosuria. No instance of affecting the renal threshold for sugar has been reported in protein calorie undernutrition. The reverse case of increase of renal threshold occurs only in diabetes Mellitus and other hyperglycemic states induced by imbalance of thyroid and pituitary hormones.

The oral glucose tolerance test showed a first hour glycemic response higher than usual in the children of the same age and also than in the same children after clinical recovery. Whereas in normal children the first hour blood sugar concentration was 52 ± 10 mg% more than the fasting level, in kwashiorkor the 75 ± 25 mg% more than the fasting concentration. It might signify, therefore, that in kwashiorkor, the glucose after absorption was failing to stimulate the pancreas adequately to secrete enough insulin to take care of the absorbed glucose. We shall come back to this point when we shall
discuss the level of plasma insulin in these children. Furthermore, whereas in normal children the blood sugar concentration in the third hour comes back to the fasting level, in kwashiorkor it was still above the fasting level. It is quite probable, therefore, that the glycemia could not stimulate pancreas to secrete insulin.

In three highly oedematous children, the response to oral glucose administration was poor. The blood sugar only rose about 15 mg\% higher than the fasting value in an hour, and came back to the fasting level soon, afterwards. This kind of response was possibly due to an associated malabsorptive state, which was brought about by an extreme oedema of the mucous membrane. These children also showed poor xylose tolerance and had moderate amount of steatorrhea. These facts, when taken together would indicate malabsorption; such malabsorption was temporary inasmuch as when these children recovered, the oral glucose tolerance became normal as did the xylose tolerance and the children did not have steatorrhea any more.

**Intravenous Glucose Tolerance Test:**

Because of the uncertainty of absorption from the alimentary tract, intravenous glucose tolerance test
has been thought to be of greater worth than the oral glucose tolerance test. While it may be so in adults and young adults, it may not be so in infants and young children. The latter react to a glucose load in a different way when the whole amount is available to the system at an instant like in intravenous tolerance from the way when the same amount is available slowly as in oral tolerance. Furthermore, infants and children are apt to develop hypoglycemia in the later hours after a single intravenous dose. Moreover, the response varies in the same patient from day to day. Despite these objections, intravenous glucose tolerance test has been advocated as the test of choice in diabetes.

Whereas in normal children the blood glucose concentration reached the fasting level in 45 minutes to an hour, in kwashiorkor the mean blood sugar stayed at a level higher than the fasting even at two and a half hours. In some children who appeared to be very sick the level at 2 hours was more than 35 mg per 100 ml. higher than the fasting level. In the majority of the children the intravenous glucose tolerance appeared to be normal. In the three cases who had flat oral glucose tolerance curve showed normal intravenous glucose tolerance; in these children, therefore, the defect in the oral tolerance
was due to malabsorption. In all the cases of marasmus, which were investigated the intravenous glucose tolerance test yielded normal values.

The fact that some cases of kwashiorkor do not handle glucose properly whereas marasmic cases do, however, should not be interpreted as a fundamental difference between the two. The defect in the handling of glucose in kwashiorkor is present only in some cases who are more severely ill. The majority of the cases do not have any defect.

**Epinephrine Tolerance Test in Protein Calorie Undernutrition**

Epinephrine causes activation of adenyl cyclase leading to the production of adenosine 3' 5' cyclic monophosphate (CAMP). The cyclic AMP converts phosphorylase b to phosphorylase a which breaks down glycogen to glucose-1-phosphate which is converted to glucose-6-phosphoglucomutase. The glucose-6-phosphate becomes converted to glucose by the liver glucose-6-phosphatase. Therefore, administration of epinephrine is associated with a rise of blood sugar. Epinephrine also causes inhibition of glucose utilization by the peripheral tissues by a membrane action acting antagonistically to insulin. The combined, glycogenolytic action and blockage of peripheral utilization causes ultimately hyperglycemia in persons injected with
epinephrine.

In the children suffering from kwashiorkor the epinephrine tolerance was subnormal. The average rise of blood sugar was only $24.3 \pm 2$ mg per 100 ml above the fasting level. In marasmus, on the contrary, the epinephrine tolerance was higher than normal $62.6 \pm 12.6$. In none of the patients, acetomuria could be detected. The subnormal response in kwashiorkor might be due to a) depletion of glycogen store or b) hepatic inability to mobilise glycogen or c) failure to block peripheral utilization. The supernormal response in marasmus cannot be readily explained. It may be due to a) unusual lability of liver glycogen or b) more complete blockage of peripheral utilization. Both the subnormal response in kwashiorkor and supernormal response in marasmus were corrected after adequate nutritional rehabilitation. Similar altered response to epinephrine in kwashiorkor and marasmus was also noted by Jaya Rao and Srikantia (Rao, 1965).
PERIPHERAL UTILIZATION OF SUGAR IN PROTEIN-CALORIE
UNDERNUTRITION IN CHILDREN:

Some of the abnormalities in carbohydrate metabolism
in kwashiorkor, like the sustained hyperglycemia after
either oral or intravenous glucose tolerance test might
be due to a slowing of peripheral utilization of glucose.
A crude way of testing the peripheral utilization consists
of simultaneous determination of blood sugar in the arte-
rial and venous blood, provided the blood flow through
the tissues is normal. Such tests as shown in Table 3, show
that peripheral utilization of sugar is subnormal in kwa-
shiorkor and either normal or higher than normal in maras-
mus. The only difficulty in the interpretation of the low
peripheral utilization of sugar in kwashiorkor lay in the
fact that the defect was present even though the fasting
blood sugar was within normal limits and the intravenous
glucose tolerance was normal in some of the cases. Thus,
if the sustained hyperglycemia in kwashiorkor was due to
low peripheral utilization why was the defect present in
children who had normal intravenous glucose. Perhaps,
glucose was diverted to other metabolic channels in the
latter cases and the diversion was enough to take care
of the extra glucose load. The peripheral utilization
as measured by the arteriovenous difference in the con-
centration of sugar few example in femoral artery and
vein concerns mainly the metabolism of sugar by the
muscular tissues. The muscular tissues are greatly
reduced in kwashiorkor and therefore the smaller
arteriovenous difference in kwashiorkor might be due to a reduced muscle mass. But this explanation is also untenable in view of the fact that muscle mass is also reduced in marasmus, but there is no reduction in peripheral utilization of sugar. These appears, therefore, to be a fundamental defect in the utilization of sugar in kwashiorkor irrespective of the clinical severity of the case.

PLASMA INSULIN ACTIVITY IN PROTEIN-CALORIE UNDERNUTRITION IN CHILDREN:

Since utilization of glucose by peripheral tissues was defective in kwashiorkor and normal in marasmus it was instructive to know the plasma insulin levels in protein calorie undernutrition in children. The insulin level in the fasting plasma was found to be not lower than normal in either in kwashiorkor or in marasmus. This is in contrast to the findings of Baig and Edozien (1965) and Hadden (1967). The former authors reported that the fasting plasma insulin levels were low in kwashiorkor and there was a normal insulin response to glucose. The latter reported that the levels were low in marasmus but normal in kwashiorkor. Other authors have shown that the plasma insulin level was low in protein calorie undernutrition in children (James and Coore, 1970; Milner, 1971).

At the National Institute of Nutrition, plasma insulin levels were found to be in the normal range on admission;
however there was no increase of insulin after oral
administration of 2 g of glucose per Kg of bodyweight,
although there was a 200% increase of blood glucose
after 1 hour. (Rao and Raghuramulu, 1972). It appears,
therefore, that some workers and ourselves found normal
insulin level in kwashiorkor and marasmus while others
observed low levels in kwashiorkor and administration
of glucose failed to raise the plasma insulin level
adequately.

The normal plasma insulin level in kwashiorkor in
the presence of low peripheral utilization of glucose
may mean either that the insulin was failing to facili-
tate permeation of glucose and to stimulate the enzymes
or the insulin was in such a state that it was not biologi-
cally active. It might be present as a proinsulin or it
may exist as a monomer instead of the usual polymeric form.
It is not possible to say which of these possibilities
is present in the child suffering from kwashiorkor.
ADRENOCORTICAL FUNCTION IN PROTEIN-CALORIE UNDERNUTRITION IN CHILDREN:

Chronic undernutrition like kwashiorkor, marasmus and nutritional edema differs from acute undernutrition like starvation in that in the former condition the organism gets time to get adjusted to the adverse dietary condition. A major part of the adaptation is mediated by hormones, especially the adrenocortical hormones. The metabolism and concentration of adrenocortical hormones are, therefore, one of the essential parameters of study in order to understand the basic mechanism of the derangement of metabolism in protein calorie undernutrition.

Some say that kwashiorkor is caused by feeding carbohydrate rich protein poor diets and marasmus by general restriction of diet (Mukherjee, 1967); others maintain that kwashiorkor and marasmus represent two ends of the same kind of dietary restriction (Gopalan, 1968; Scrimshaw and Taylor, 1964). If there is a pattern of dietary restriction leading to kwashiorkor and another pattern producing marasmus, will that lead to a difference in the adaptation of the patient to the particular kind of diet. And will that lead to a difference in the hormonal level in these children, especially the adrenocortical hormones?
It appears from earlier studies and also from the present investigations that the level of plasma cortisol is increased in protein calorie undernutrition in children (Leonard and MacWilliam, 1964; Alleyne and Young, 1967; Jayarao, Srikantia and Gopalan, 1968; present studies). It did not matter whether the child was suffering from marasmus or kwashiorkor, plasma cortisol level was found to be high. The response to ACTH was also found to be normal (Alleyne and Young, 1967, Rao, Srikantia and Gopalan, 1968). Although previous workers thought that the high plasma level was caused by stimulation of the adrenal cortex to the point of exhaustion (Castellanos and Arroyave, 1961). An ingenious interpretation has been brought out by Rao, Srikantia and Gopalan that in classical kwashiorkor the failure of the adrenal cortex to respond to ACTH, may be responsible for some of the particular clinical manifestations.
It is known for about 100 years since Claude Bernard described liver glycogen that starvation is associated with a decrease in amount of glycogen in the liver. Chronic undernutrition in children, was reported to cause an increase of liver glycogen by histochemical and compositional studies (Waterlow & Weisz, 1956; Salazar de Sousa, 1959). Later on, however, it was found that the amount of glycogen was reduced in protein calorie undernutrition (Alleyne and Scullard, 1969). The present observations also indicated that the liver glycogen was decreased in amount in all three types of protein calorie undernutrition.

Glycogen has been thought to be a compound which is not essential to life. Nevertheless, some amount of glycogen is present in all tissues and in all periods of life, even in a fetal stage. In vivo it exists in a polydisperse form and its molecular weight ranges from $2 \times 10^6$ to several hundred millions. The advantage of such very large molecular weights is obviously one of storage without appreciably adding to the oncotic pressure inside the cell, especially in view of the easy solubility of glycogen in water. In undernutrition when there is a decrease in the amount of glycogen, several questions come to our mind.

1) Is there an irreducible minimum, below which the liver glycogen cannot be reduced?
2) Is there a tendency for the glycogen to exist in low molecular weights under such circumstances?

3) Is the remaining glycogen structurally normal?

As regards the first question, the answer is there is no irreducible minimum in the amount of liver glycogen. Although in most of the cases, the liver glycogen was around 2.3 g%, in quite a few cases the glycogen content came down to as low a value as 0.4 g%. Furthermore, there were three children in whom the liver glycogen content was found to be inestimable, i.e., there was no coloration with anthrone reagent. It was true, of course, that the latter cases were very moribund and did not survive even 24 hours of hospital stay.

As regards the second question i.e., whether liver glycogen in protein calorie undernutrition has relatively low molecular weights, we do not know the answer. In experimental animals, however, it was found that the liver glycogen consisted predominantly of relatively lower molecular weights (Orrel, Bueding, & Reissig, 1964). Because of the higher degree of hydration of the tissues in protein calorie undernutrition, it is probable that the physical structure of glycogen may include in its interior some water molecules which prevent adequate packing and hence would facilitate lower molecular weight.
The liver glycogen which was left in protein calorie undernutrition in children had normal structure as shown by the absorption spectrum of the color produced by the addition of iodine to the solution of glycogen.

The muscle glycogen was also reduced to about half of the value obtained after clinical recovery. There were occasional cases where the liver or the muscle glycogen content was either normal or abnormally low. That made the standard deviation rather high. Such values also make it appear that there is no fundamental relation between the protein calorie undernutrition and the glycogen contents. The actual value obtained in a particular child depended on so many associated factors that it was impossible to predict which child was likely to have what amount of either the liver or muscle glycogen.
HEPATIC ENZYMES BREAKING DOWN LIVER GLYCOGEN IN PROTEIN CALORIE UNDERNUTRITION IN CHILDREN

There are four enzymes which break down glycogen to glucose, phosphorylase, amylo 1:6 glucosidase, phosphoglucomutase and glucose-6-phosphatase. Besides, an amylase also splits glycogen. Of these enzymes we have measured phosphorylase and glucose-6-phosphatase activities in the liver and phosphorylase activity in the muscle.

The phosphorylase activity of the liver on admission of the children as well as on recovery in both kwashiorkor and marasmus was more or less the same. The reaction catalyzed by the enzyme is readily reversible but it is thought that in vivo the enzyme is only concerned with glycogen breakdown. The method that we have used for the estimation of the activity in vitro employs glycogen synthesis rather than glycogen breakdown. Is it possible that an enzyme which readily catalyzes a reaction in both ways can be affected differentially under these conditions? Or in other words can a forward reaction be affected in preference to backward reaction? The forward reaction in this case will produce more glucose-1-phosphate and backward reaction more glycogen. The activation of phosphorylase b to phosphorylase a by means of glucagon and epinephrine through the second messenger cyclic adenosine 3'-5'-monophosphate has mostly been studied with respect to breakdown of glycogen to glucose-1-Phosphate.
However in protein calorie malnutrition, we do not
know whether the phosphorylase activity as measured by the
method we used, really related to the synthesis or break­
down of glycogen. The fact that the activity of this
enzyme was similar on admission and before discharge
does not vouchsafe the glycogen was being normally broken
down in protein calorie undernutrition.

In kwashiorkor, glucose-6-phosphatase activity of the
liver was found to be reduced on admission of the children
as compared to the activity found before discharge. In
marasmus, however, the values found on admission and
before discharge were comparable. Mukherjee & Nath (1957)
as well as Fletcher (1966) and Salazar de Souza (1959)
found a reduction in the activity of the enzyme whereas
Alleyne & Scullard (1969) observed an increase. The pre­
sent observations not only showed that, in general, the
activity of the enzyme was decreased but also the activity
was nil in two fatal cases. By and large those cases of
kwashiorkor who had low fasting blood sugar also had low
glucose-6-phosphatase activity in the liver. It, therefore,
appears that a reduced liver glucose-6-phosphatase in the
presence of low liver glycogen is probably responsible for
the hypoglycemia found in such children.

In vivo, under natural conditions, glycogen is not
synthesized by phosphorylase but the enzyme UDPG-glycogen-
glucosyl transferase, in short, glycogen synthetase,
discovered by Luis Leloir in 1957 (Leloir, 1964). The activity of this enzyme, was measured according to the method of Barber (1967) in liver homogenates obtained after needle biopsy. As mentioned earlier the minimum amount of tissue required for estimation of measurable activity was 30 mg; this relatively large amount of tissue could be obtained by needle biopsy of the liver in only kwashiorkor with ease; in marasmus such amount of tissue could be gotten only in a few cases. From such data as we have, it appears that glycogen synthesis was not affected in kwashiorkor since the values on admission and before discharge were more or less the same ($p < 0.5$). Since glycogen contents, on admission, were half of the contents before discharge and since both glycogen synthetase and glycogen phosphorylase activities were normal it appears that UDP-glucose is the rate limiting factor in the reaction. The biosynthesis of UDPG may, therefore, be profitably studied in these patients. Since the number of marasmic children that could be studied was very small, it is not possible to draw any inference from the estimation of glycogen synthetase.

In the muscle, in contrast to the liver, the phosphorylase activity, on admission of the children, was low in both kwashiorkor and marasmus. Glycogen synthetase activity was also low at this time. It appears, therefore, that the low glycogen content of the muscle was due to decreased glycogen synthetase activity,