The human life span is generally divided into some periods or natural divisions by the physiologists, according to growth, maintenance and decay. The term 'Child' literally means "the human young from infancy to puberty". But in conventional practice it is usually referred to the period from early months of life up to late pre-school age.

In Latin nutritio means to nourish. Nutrition is the "combination of processes by which the living organism receives and utilizes the materials necessary for the maintenance of the functions and for the growth and renewal of its components." (Turner, 1959). The nutrients as ordinarily referred to, include water, carbohydrate, fat, protein, vitamins and inorganic elements.

Undernutrition may, therefore, involve a reduced intake of any of these constituents singly or in combination. In the present context, however, we would be considering only undernutrition due to reduced intake of calories and protein. Such undernutrition is a major contributing factor to the high mortality and morbidity in early childhood in developing countries and "is the most serious and widespread nutritional disorder known to medical and nutritional science" (Brock & Autret, 1952).
It may theoretically be due to a total calorie deficiency or predominantly protein deficiency but in most instances a combination of both calories and protein exist in a particular case.

Calorie is a unit of energy and is defined as the amount of heat required to raise the temperature of water from 14.5° to 15.5°. Since all forms of energy are interconvertible it does not really matter in what unit the energy is expressed. But currently, attempts are being made to use Joule as the universal unit of energy rather than have alternate units of energy like calorie. But since the term calorie has been in use for a pretty long time in connection with nutritional research, this term is retained and used in the present thesis, although International Union of Nutritional Sciences would prefer the substitution of Joule for Calories.

Undernutrition can occur in children with respect to deficiency of calories and/or protein in the diet. However, a situation in which the inadequacy is only with respect to either calories or protein only, is highly artificial and does not occur under practical conditions. However, there is no denying the fact that if the total dietary intake is inadequate, the resulting syndrome in children most frequently leads to what the clinicians describe as marasmus. And if the diet consumed is predominantly starchy and very deficient in protein like that provided by Sago or even Barley, for
a long period of time, certainly, the children do develop classical kwashiorkor. However, even now, the clinicians do not agree over the minimum criteria necessary for the diagnosis of kwashiorkor. If we accept that any case of edema, developing in the course of protein calorie undernutrition is sufficient for the diagnosis of kwashiorkor, then there is no justification for calling an undernourished child as suffering from marasmus or kwashiorkor since edema may come and go in any child suffering from malnutrition depending on some other environmental situation. However, more would be said about this aspect later on.

The clinical condition arising as a result of grossly inadequate diet is called marasmus. According to Smellie (1954) the term 'marasmus' was first introduced in 1600 by Soranio to describe the condition of infants who were suffering essentially from starvation. The extremely low calorie diets responsible for the syndrome are obviously also deficient in proteins and many other essential nutrients, but calorie is the main factor that counts. Marasmus is tending to occur increasingly frequently, associated with diarrhoeal disease, in artificially fed infants in towns in developing regions of the world (Jelliffe 1962a; Cronje et al, 1963; Graham & Morales, 1963; McLaren, 1966).
The marasmic children is generally described as being reduced to "skin and bones". This condition may occur at all ages, including childhood (Jelliffe, 1968), but it is seen most commonly in the first year of life. In marasmus, growth stops, but no serious metabolic disturbances are observed. Despite the generalized wasting, the child remains clinically alert and maintain a good apetite.

The term "Kwashiorkor" was used by Dr. Cicely Williams (1935) to describe a disease occurring in a young child displaced from his mother by the next succeeding sib. In the Ga language from which the term originates, Kwashi meant first and orkor second, or the sickness of the first caused by the second. The term kwashiorkor is currently used almost universally for this particular extreme form of protein calorie undernutrition in early childhood, even though there is disagreement as to the minimum diagnostic criteria. Kwashiorkor can occur in infancy or in later childhood, and even in adult life, although this is rare.

Breast milk is the mainstay of protein nutrition for the first six months of life and is usually all that is needed for this period. At weaning, the child is generally placed on an artificial formula based on for example, cow's milk, and gradually weaned on to mixed feeding, characteristic of the community. But in underprivileged
communities or among ignorant and socially depressed groups, and in city slums the child is put on a diet rich in starchy calories but deficient quantitatively or qualitatively in protein — for example cooked plain-tain, sweet potato, cassava, sago etc.

The majority of deaths in these severely undernourished children occurs during the first year; many of the babies which survive the first year of life develop kwashiorkor in their second or third year. There is nothing dramatic about the onset; the baby does not suddenly go downhill, but rather seems to creep into a state of kwashiorkor without ever having been well since the age of six months (Waterlow, 1956). In this way develops a classical kwashiorkor. The mortality of children from one to four years old in a country is the index of seriousness of protein malnutrition (Bengoa et al, 1959). Protein-calorie malnutrition is worldwide in distribution and areas most affected include the countries where large proportions of the population are living under conditions of limited social and economic development (Scrimshaw & Behar, 1965).

There is a widening gap between the growing world population and available food supplies (Sen, 1965). But hunger demands a full stomach, and the ease and cheapness of production of carbohydrate rich foods, tend to keep diets low in protein and fat, except when economic circumstances allow.
The scene is now set for protein malnutrition. In countries where protein is in short supply the growth of infants tends to fall off by the age of about 6 months. Infants grow well during the first five to six months of life, when the supply of breast milk is adequate for their needs. Somewhere between the sixth and the twelfth months, growth in the majority of children ceases to be satisfactory. Clinical signs of protein malnutrition appear towards the end of the 1st year or 2nd year of life, the average age of onset varying a little according to the local dietary pattern. Thus of 1141 cases analysed by Trowell, Davies & Dean (1954), 45% were in children between 1 and 2 years of age, and 69% in children between 1 and 3 years of age. " ..For every child who become clinically ill there are undoubtedly many more in a state of marginal protein malnutrition" (Chan & Waterlow, 1966). In population where food is in short supply, it is the children who suffer most. It is due to an unequal distribution, the younger the child, the smaller its share in the family pot, and many foodstuffs are also forbidden to him. There are many reasons but most of them are due to mother's ignorance of the nutritional needs of children and ways to satisfy them, and from unfortunate cultural beliefs and taboos (Jelliffe 1955 and 1957). Thus in spite of much higher requirements for protein and calories the child receives less than his parents per kg. of body weight.
(Martínez, 1951). In this fashion starts the characteristic history of infant undernutrition.

Thus the nutritional status of young children as regards proteins and calories may be viewed as a continuous gradation from 'normal' through mild and moderate degrees of malnutrition, to advanced syndromes, of which the two most important are kwashiorkor and marasmus (Jelliffe, 1959). The term 'protein-calorie undernutrition' was introduced in an attempt to attach an etiologically helpful label to the group as a whole and should be used to cover the whole range of classifiable and unclassifiable manifestations of inadequate protein and calorie intake (Jelliffe, 1959).

Some group of workers proposed that the term "Protein-calorie undernutrition" be replaced by two terms protein deficiency and calorie deficiency to recognize the differences between kwashiorkor (protein deficiency) and marasmus (calorie deficiency). They feel that both conditions can now be produced experimentally and the term 'protein-calorie undernutrition' covering a variety of syndromes has often prevented a search for a more exact diagnosis (Bradfield, 1968).

But the clinicians from Africa, Lebanon, and Jamaica suggested that the term 'protein-calorie undernutrition' be continued as a generic expression to cover a wide range of malnutrition on a community basis with the understanding that it is not diagnostic for the individual malnourished child.
The FAO/WHO Joint Expert Committee on Nutrition (1962) also proposed the term 'protein-calorie malnutrition' to cover diseases such as marasmus, kwashiorkor and famine oedema. The term continues to have the advantage of emphasizing the need for both protein and calories, in the diets of young children and also in the therapy of all forms and degrees of protein-calorie malnutrition, including the two severe syndromes of kwashiorkor and marasmus. Whereas if the term "Calorie deficiency" were to be used for human marasmus it might mislead medical and other health personnel that calories were the only important item with a potentially disastrous possibility that the calorie gap may be bridged by sugar or starch.

Secondly though clear cut polar cases occur, most children have mixed deficiencies, either as intermediate severe syndrome or more usually, as mild to moderate forms which defy precise nomenclature. The protein deficiency and calorie deficiency either may occur simultaneously with one or other predominant or can, as it were, develop 'in series' with one primary and initial and the other secondary and supervening (Jelliffe & Stanfield, 1966).

Besides, protein and calories are always interdependent (hence the hyphen) in protein-calorie deficiency (Platt, 1966).

Moreover there is much protein-calorie deficiency which would not be diagnosed if 'the two syndromes' were the only ones recognised (Platt, 1966).
'Protein-calorie undernutrition', however remains a useful descriptive term for the overall problem, particularly in the teaching of its prevention in the community and public-health fields. All the same, individual children with protein-calorie undernutrition always need more specific diagnosis and grading into mild, moderate or severe degrees of involvement, and in the last group, into the identifiable syndrome of kwashiorkor and marasmus where possible (Jelliffe, 1968, Mukherjee, 1967).

To an extent in children more than in adults, protein malnutrition is associated with caloric deficiency. Therefore, the typical kwashiorkor syndrome is seldom seen in adults, although occasional reports of this syndrome appear in the literature especially in conjunction with chronic debilitating diseases, gastro-intestinal absorption defects, food faddism, and alcoholism. Sometimes an adolescent with chronic infection or a lactating woman will show acute kwashiorkor like syndromes.

Hunger or famine oedema is seen in areas of the world where chronic severe protein-calorie malnutrition is endemic, or after a population group is exposed to severe dietary restriction for several months. The diet in the period preceding the illness has almost always been largely carbohydrate with little protein or fat, and has always been very plain and monotonous.
In a comparative study of malnourished adults with edema and children with protein calorie undernutrition, growth is of primary consideration. The adult, as they already have their full stature, the body size are not affected though they become thin and have extreme muscle wasting. While in case of children, the disease sets on during the growing period and there is a failure of normal growth, affecting especially weight and height for age.

The dyspigmentation and the change of texture of hair is an event in kwashiorkor in children. The hair becomes thin, pale, stiff and curly and can be removed by a slight pull without any pain.

In case of adult it shows some change no doubt but of lesser degree than children. It is almost always soft; it loses most of its curliness and toughness, and its sheen. The change in colour is most obvious on the forehead but can also be seen on the limbs and trunk. The eyelashes, eyebrows, moustache and beard and the supra-pubic hair are very resistant to the change of colour.

Enamel paint dermatosis is another important characteristic of acute kwashiorkor in infants. Dermatosis is very rare in adults, although some degrees of dryness and roughness is very common and 'crackled skin' occasionally covers large areas of the body. Though this is of rare occurrence,
Brown & Trowell (1944) observed the typical kwashiorkor dermatosis in an African adolescent and also in Polish women refugees.

The effects of calorie or of protein deficiencies, or of both in adults has been amply reviewed by Trowell et al (1954), Widdowson & Dickerson (1964) and Viteri et al (1964). Severe malnutrition in adults is still indigenous in some countries such as India (Monckeberg, 1956), and Africa (Gomez, 1958; Stamer, 1954; Brock, 1954) or incidental to the tyranny and oppression of war upon selected population groups, as in Germany during and after the second World War (McCance, 1951). Severe undernutrition also has been produced experimentally in normal young male volunteers (Keys et al, 1950) and studied in mental patients who refused to eat or had anorexia nervosa (Ljunggren, 1957; Elkitin, 1959). In general, protein deficiency is associated with calorie deficiency to a greater extent in adults, although oedema and skin changes have been observed in adults with advanced undernutrition. The compositional changes in severely malnourished adults with respect to water and electrolytes are similar with those of children with PCM (Viteri et al, 1964). The liver iron and nitrogen contents and catalase, cholinesterase, and alkaline phosphatase activities are similar; serum protein changes are somewhat less severe but serum
enzyme changes are similar in children with kwashiorkor and in malnourished adults with oedema (Mukherjee, 1953). The hypofunction of the endocrine glands may be exaggerated in adults (Zubrian, 1955).
The name "Carbohydrate" is based on the generalization that these compounds have the empirical formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and hence the French applied the name "hydrate de Carbone" or Carbohydrate, and the name has been retained even though it is not descriptive. As because there are many other compounds which has the formula $C_n(H_2O)_n$, but which are not carbohydrates for example acetic acid ($C_2H_4O_2$), and lactic acid ($C_3H_6O_3$). And there are other carbohydrates such as rhamnose, $C_6H_{12}O_5$ which does not fall in the above formula. The class of compounds designated as carbohydrates includes polyhydroxyaldehydes, polyhydroxyketones and substances of higher molecular weight which yield these compounds upon hydrolysis. In reality they are aldehyde or ketone derivatives of polyhydric alcohols.

The entire network of reactions in the organism involving compounds which interconvert carbohydrate constitutes carbohydrate metabolism. In the animal body it is essentially the metabolism of glucose and of substances related to glucose in their metabolic processes.

In all ordinary diets and invariably in famine, the largest share of the caloric intake is supplied by the carbohydrates. Moreover, a fair amount of protein metabolized by the adult passes through the same oxidative pathway as the carbohydrates. Even the fats, through
their participation in the citric acid cycle, are brought into closer alliance with carbohydrate metabolism. The fact that the human body has only a limited carbohydrate reserve lends further importance to the subject of carbohydrate metabolism in starvation and famine. Although most of the steps in the oxidation of carbohydrates are in general known, the exact stages which are affected by different types and grades of undernutrition are still currently under active studies in many laboratories of the world.

CARBOHYDRATE METABOLISM IN EXPERIMENTAL ANIMALS

Digestion and Absorption of Glucose

Restriction of food intake has previously been shown to have a depressing effect on mitotic activity in several tissues, including the intestinal crypts (Diller & Blauch, 1946; Bullough and Bisa, 1950; Bullough and Ebling, 1952; Leblond and Stevens, 1948; Loeb et al, 1939; Widner et al, 1951). In one of the earliest reports on experimental fasting in animals, Sun reported that 48 to 72 hour of total fasting produced distortion of intestinal epithelium and loss of villous structure in the mouse (Sun, 1927). Diller and Blauch also found a decrease of about 80 per cent in the mitotic activity of small intestinal epithelium in mice which had been starved almost to death (Diller and Blauch, 1946). In case of fats (starved for 5 days) it was found that the population of cells lining
the crypts and villi was moderately reduced in starvation, although the duodenal mucosa of starved rats revealed a normal appearance as compared with those of control fed animals (Stevens and Blair, 1958). Brown et al. (1963) demonstrated a reduction of mitotic activity in the intestinal crypts of fasted rats with decreased intestinal epithelial cell renewal and migration rate. Heller (1954) found no histologically demonstrable lesions in the small intestine of the fasting (for 48 hours) animals. Cori and Cori (1927) found that both glucose and fructose absorption were reduced in rats fasted 24 or 48 hours. This general observation was later confirmed by several other workers (Marrazzi, 1940; Magee, 1945; Heller, 1954; and Crouzlon-Bourcart, 1968). Heller (1954) while studying the intestinal absorption in rats, showed decreased intestinal absorption of glucose in rats starved for 48 hours; there was no delay in gastric emptying time. Rats deprived of food for 96 hours showed in most instances an accelerated discharge of glucose from the stomach; the absolute amounts absorbed from the intestine were much the same as those in the controls. Fasting for 72 hours in rats has been associated with a decrease in sucrase activity (Blair et al., 1963) and alkaline phosphatase activity (Tuba, 1953). Feeding sucrose to fasted rats resulted in a greater increase in sucrase than maltase activity and the converse was true.
with a maltose diet (Deren et al, 1967).

Semi-starvation or reduction in food intake, has the opposite effect. Intestinal absorption of glucose was not diminished in undernourished rats (Halmi, 1956). Kershaw, Neame and Wiseman (1960) showed that there was a striking increase in the capacity of the intestine from semi-starved rats to absorb both glucose and histidine compared with control both in vivo and vitro. The entire intestine of the semi-starved rats had about twice the capacity of the control to absorb glucose. Hindmirsch et al (1967) further showed that in the rat and guinea-pig semi-starvation resulted in increased active transport in all regions of the small intestine compared to normal. No alteration in active transport was observed in the hamster under such circumstances. Esposito (1967) showed increase absorption of glucose but not of 3-O methyl glucose in the intestine of semi-starved rats compared to normals. It was also observed (Neale, 1968) that the intestine of semi-starved rats could transport L-glucose against its concentration gradient while the sacs of intestine from normal fully fed rats could not. While complete starvation causes a fall in the levels of hydro-lytic enzymes in the intestine, Lojda and Fabry (1959) showed that intermittent starvation resulted in an increase of both alkaline phosphatase and esterase in the upper intestine.
Experimental evidence that protein deficiency causes the structural and functional alterations of small intestine has been reported in pigs by Platt et al. (1964) in rats by Takano (1964) and rhesus monkeys by Deo and Ramalingswami (1964). Histological studies revealed a normal appearance of epithelial cells but a shortening of the villi and a decrease in the number of cells in the crypts. The mechanism of these morphological changes of the villi was investigated (Deo and Ramalingaswami, 1967; Hooper et al., 1968) and a few reports on enzymatic and ultrastructural studies of jejunal mucosa in protein depletion (Solimano et al., 1967; Hill et al., 1968; Prosper, et al., 1968) was available. Recently Tandon et al. (1969) reported that the ultrastructure of the microvilli was not altered nor were there changes in the brush border enzymes examined. Acid phosphatase and succinic dehydrogenase activities were significantly reduced, although the mitochondria appeared normal in fine structure. Hill et al. (1968) also reported that mitochondria were normal in the absorptive cells of the rat jejunal mucosa after 20 days of protein-free diet. He also reported that a 20 day protein-free period did not alter the microvilli of the epithelial cells in the rat jejunum. Glucose-6-phosphatase activity was unchanged, and this correlated with the maintenance of the rough endoplasmic reticulum. This also correlates with earlier biochemical studies which showed that the protein and RNA content of the intestinal epithelial cell was not altered in protein depleted rats (Munro et al., 1964).
Atrophy, fibrosis, and alteration in function of the pancreas have been observed in experimental animals kept on a protein deficient diet (Ramalingaswami, 1964). These abnormalities appear in the experimental animal within two weeks of initiating a protein deficient diet (Suzzane and Iber 1967; Veghelyi et al, 1950; Weisblum et al, 1962; Paradisi, 1965; Rothman, 1969) and are associated with a striking reduction in pancreatic secretion (Suzzane and Iber 1967). Robbercht (1967) also found a reduced activity of pancreatic RNase, trypsinogen, chymotrypsinogen, lipase and amylase in young rats maintained on low protein diet. Among children deprived of protein for only 3 weeks, marked reduction in basal pancreatic flow was recorded (Veghelyi, 1950). These studies served to point out the rapidity with which functional and morphological alterations occurred in the pancreas following protein deprivation in both man and experimental animals. The importance of associated vitamin or mineral deficiency in initiating pancreatic exocrine dysfunction is not known at present.

Barbezat (1967) did not find any decrease of bicarbonate concentration of pancreatic juice in animals fed a low protein diet. Complete functional recovery took only 3 to 6 weeks following initiation of a high protein diet in experimental animals (Suzzane and Iber, 1967).
The results on animals on protein deficient diet showed that the mean amounts of glucose that disappeared from the gastrointestinal tract during a standard period were reduced in protein-deficient animals (Heller, 1954). He also showed the discharge of glucose from the stomach was significantly retarded and agreed with the observation of Mecray, Barden and Ravdin (1937) who found a delay in gastric emptying time in hypoproteinaemic dogs, but it differed from the results of Beams, Free and Leonards (1944) who failed to find it in dogs having edema and associated low plasma-protein level. Opuszynska (1966) found very active thiamine-pyrophosphatase activity in the intestine of protein deficient rat. Solimano et al (1967) showed that disaccharidase activity of the jejunal mucosa increased after feeding a low-protein or protein free diets to rats, while Jacques et al (1968) found no consistent differences in the activities of disaccharidase between the control and rats deprived of protein.
BLOOD GLUCOSE

Absorption of glucose from dietetic sources, hepatic breakdown of glucose and formation of glucose from non-carbohydrate forms on the one hand, and glucose utilization by tissues and organs on the other, determine the amount of available glucose at any particular time. The concentration of glucose in the blood is an index of these two processes, one favouring ingress of glucose into the blood and the other favouring egress. Under normal conditions of metabolism, the rate of entry into and the rate of disappearance from the blood are approximately equal as a result of which the concentration in the blood does not have much variation. This dynamic equilibrium is reasonably well maintained.

The glycemic state has, therefore, been an object of study from earliest times of clinical biochemistry. Earlier attempts of such study was hampered by the lack of a suitable method of glucose determination. But when a reasonable method was available, a flood of studies began to pour in on the effect of inanition on the blood sugar. Thus Von Merring (1877) studied the effect of starvation on blood glucose in dogs and found it to have no influence. Later workers, however, showed that acute starvation caused a decrease in the level of blood sugar (Otto, 1885, Shope, 1927; Hershey and Orr, 1928; Parnatt, 1966). A difference
A difference was elicited with respect of starvation induced hypoglycemia and the age of the animal. In newborn pigs, blood glucose levels fell within 72 hours of fasting to hypoglycemic levels; in contrast, 4 day and 1,2 and 3 week old animals maintained normal blood glucose levels after a similar period of starvation (Kenneth, 1968).

The fasting blood sugar of underfed rats were significantly higher than normally fed rats. However, 5 gm glucose/100g were administered, after 24 hours fast and tested 8 hours later, they showed a lower blood sugar than normals (Halmi, 1956). In experimental studies with kwashiorkor like models, fasting blood sugar was reported to be similar to that of the controls (Wilfred, 1967; Sidransky, 1958). But Heard (1966) reported hypoglycemia in experimental animals, subjected to chronic malnutrition.
GLUCOSE TOLERANCE

Although glycemic condition has been the usual parameter of study of carbohydrate metabolism, an abnormal blood sugar level alone reveals little about the particular defect in the metabolism, whether absorptive, assimilative, storing, mobilizing or utilization.

Tolerance tests are designed for more functional examination of carbohydrate metabolism. The rise in the blood level of a particular sugar (glucose, levulose, galactose) and its removal from the blood is determined after oral or intravenous administration of a standard dose. The definition of "normal" glucose tolerance is indicated by the W.H.O. Expert Committee on Diabetes (1965). By glucose tolerance is meant the rate of removal of intravenously administered glucose from the blood. After initial equilibration of glucose in the extracellular space, its removal proceeds like a first-order reaction in the \( dc/dt = KC \). Hence if the blood glucose concentration in mg/100 ml is determined at intervals after the injection of glucose, and then plotted on a logarithmic scale against time in minutes \( t \) the points should fall on a straight line, the slope of which is a measure of the glucose tolerance i.e. \( K \), which is calculated from the equation

\[
K = \frac{2.3(\log C_1 - \log C_2)}{t_2 - t_1} \times 100
\]
where $C_1$ and $C_2$ = glucose concentration at times $t_1$ and $t_2$ respectively (Ikkos and Luft, 1957).

The normal pattern of glucose tolerance in animals and humans is low at birth (Heard et al, 1961, Baird, 1962), followed by a marked rise during the period of rapid growth reaching a peak in early adult life and thereafter declining slowly but steadily (Himsworth, 1939; Loeb, 1961).

From a series of observations on groups of animals receiving different diets it appeared that the degree of glycemic response might be related to the previous dietary history of the animal.

More than 50 years ago Von Noorden (1905) pointed out the ability of an animal on oatmeal diet to 'cure' severe glycosuria in diabetes. Himsworth (1933, 1934, 1935) in a series of investigations reported the intensity of the glycemia in a glucose tolerance test to be inversely proportional to the amount of carbohydrate in the previous diet. He also reported that the tolerance is impaired by fat and unaffected by protein (Himsworth 1939). He further demonstrated an analogous effect of diet on the glycemic response to insulin. Uram, Friedman and Kline (1956) showed that on a casein sucrose diet the blood glucose levels approach 200mg per cent as
compared to the 120 mg per cent on a cereal ration. Hales (1963) found that short term restriction of dietary carbohydrate may impair glucose tolerance for several weeks.

As impaired glucose tolerance does not necessarily reflect diabetes, starvation does decrease glucose tolerance (Halmi, 1957): reports of impaired glucose tolerance in fasting and starved animals by a number of workers led even to the concept of 'starvation diabetes' (Keys et al, 1950). After a period of acute starvation the ingestion of carbohydrates produces an alteration in the subsequent blood sugar curve and in urinary sugar excretion (Hofmeister, 1890). Rabbits fasted for several days show glucose tolerance curves of the diabetic type (du Vigneaud, 1925), while rats fasted for 1-6 days failed to show a progressive decrease of oral glucose tolerance. But intravenous tolerance showed a delayed return to normal (Halmi, 1957; Orrya, 1961). The influence of the season must also be considered in the interpretation of the glucose tolerance made after starvation, at least as far as animals are concerned (Cori and Cori, 1927a, 1927b; Barbour, 1927). Heller (1954) showed no difference in tolerance in starved and control rats.

The experimental animals suffering from subclinical marginal or severe protein calorie deficiency develop impaired glucose tolerance (Heard et al, 1964; Turner et al,
GLYCOGEN

Glycogen is the main form in which carbohydrate is stored in the body. A number of workers reported that acute starvation causes a diminution of the glycogen content of the liver (Pfluger, 1907; Junkersdorf, 1921; Ling & Shen, 1934; Cori, 1926; Carrole, 1968; Herrera, 1968; and Takeshi, 1969). The low levels of liver glycogen observed in rats after 24 hours of starvation could be reduced still further by physical work (Mutter, 1941). In the recovery period following such work the exercised rats showed an increase in glycogen level to about twice that of the nonexercised controls. The lowered liver glycogen content never returned to normal under any circumstances.

An increase in liver glycogen stores during the starvation period was also observed in rats (Barbour et al, 1927; Duel et al, 1934; Mirski et al, 1938) in dogs, (Pfluger, 1907) and in fowl (Emalie and Hensh, 1933). It was shown that liver glycogen increased in rats during starvation only after the forty-eighth hour. Herrera (1968) showed that hepatic glycogen displayed the earliest reduction during fasting; it was significantly lowered after 6 hours, fell to lowest levels after 48 hours and subsequently increased again. These levels of glycogen were influenced by previous diet and sex of the animal.
Muscle glycogen was lost more slowly than liver glycogen throughout fasting (Takeshi, 1969). The muscle glycogen stores was reported completely depleted in severely starved dogs (Pfluger, 1907) with the suggestion that this reserve disappeared when the animal lost 40 percent of its weight (Michailescu, 1914).

Few studies have been made on the glycogen stores during periods of semi-starvation. Moulton (1920) determined the glycogen stores content of the liver and shoulder muscles of steers given various amounts of feed. The semi-starved animal, which was very emaciated, had as much glycogen in the muscles, on a fat-free basis, as the liberally fed animal. The glycogen in the livers of all animals, expressed as percentage of the fresh weight of that organ, showed no consistent differences.

Normal or higher than normal levels of hepatic glycogen has been observed in rats and pigs fed low protein diets (Sidransky, 1958; 1960; 1964; Heard, 1967; Heard, 1966; Ericson, 1966; Williams, 1965, Jaya Rao, 1965; Juan, 1967). At this time the glycogen, when examined after histological staining, was diffusely distributed in the liver (Sidransky, 1958; 1960; 1964). Also using electron microscopy the hepatic
glycogen was randomly distributed throughout the lobule, but most often tended in any single hepatic cell periphery, and in addition many lysomes contained large amounts of glycogen (Shinozuka, 1968). Iodine spectrum analysis on hepatic glycogen revealed no differences in control and experimental animals (Epstein, ).
Glycolytic Enzymes:

The activity of liver phosphorylase decreased to approximately 1/3rd after fasting for 96 hours and slowly returned to normal on refeeding (Gutman, 1964). Niemeyer made a similar finding that during fasting, liver phosphorylase in rats, expressed per 100g initial body weight, declined progressively in 3 days to about 40% of normal, but had not decreased further after the fourth day. On refeeding, the phosphorylase activity increased to normal during a period of time similar to that of fasting (Niemeyer, 1961). However, Takeshi (1969) found that the phosphorylase activity of the liver increased when the animals were fasted for 12 hours and the phosphorylase activity of the skeletal muscle gradually decreased during a fast of 72 hours. He also reported that both a high carbohydrate diet and a high lipid diet elevated liver phosphorylase activity but a high lipid diet decreased muscle phosphorylase activity. Fagundes & Cohen (1965) also found an increase in phosphorylase activity during the first 8 hours of starvation. Freedland (1967) found a decrease in the activity of phosphorylase on days 1, 2 and 4 of starvation. Phosphorylase activity was unchanged in adult sheep starved for 10 days (Bruno et al, 1969). However, if the animals were chronically undernourished instead of being acutely starved, the hepatic phosphorylase
activity was found to decrease (Verma, 1967; Sidransky, 1970).

In young rats phosphoglucomutase activity of liver decreased after one day of starvation and remained relatively constant during the next 3 days of starvation (Freedland, 1967). In adult sheep the activity decreased by about 1/3rd when fasted for 10 days (Bruno, 1970). Verma reported no alteration of activities of phosphoglucomutase in the experimental animal (1966).

Glucose-6-Phosphatase activity remained relatively constant during 3 days of starvation and decreased on day 4 (Freedland, 1967). The hepatic glucose-6-phosphatase markedly increased when expressed per weight basis, however, when enzymatic were expressed per average cell, it was found that glucose-6-phosphatase was maintained in the normal range during 6 days of fasting (Weber & Cantero, 1958). Fasting for 42 hours doubled the glucose-6-phosphatase activity and after 60 hours of fasting the activity increased further (Schriefers, 1965; William, 1965, 1967). Jomain (1970) also reported an increased activity of glucose-6-phosphatase during fasting. In adult sheep starved for 10 days 33% increase in activity was
observed (Bruno, 1970). Rats receiving a protein free diet showed a significant decrease in Glucose-6-Phosphatase activity (Freedland, 1959). Sidransky (1969) found no difference in the level of hepatic glucose-6-phosphatase activity in undernourished animals. Verma reported a decreased activity of liver glucose-6-phosphatase in malnourished animal (1966).

Liver transglucosylase was not affected markedly during fasting and seemed to follow changes in liver protein (Gutman, 1964). The synthetase activity was also similar in control and undernourished animals (Sidransky et al, 1970).
HORMONES IN CARBOHYDRATE METABOLISM

Although the level of blood glucose is kept within normal limits by regulating the breakdown and synthesis of glycogen in the liver and muscles, the actual regulatory process is under the influence of a number of hormones.

The role of endocrine glands, however, in the potentiation and maintenance of marasmus and kwashiorkor was largely overlooked. In 1953, Gilman and Gilbert demonstrated by endocrine ablation and hormone replacement experiments with baboons that the fatty liver, so characteristic of kwashiorkor, could have its origin in a disturbance of endocrine system involving principally a deficiency of insulin and thyroxine and an adequate supply of adrenocortical hormones. The alterations found in the pancreas (Stewart et al, 1958; Stewart et al, 1960; Heard and Stewart 1971), thyroid (Stewart et al, 1960; Platt, B.S.; 1962, Platt, et al, 1964) and adrenal cortex (Stewart et al, 1960; Durbin et al, 1962, Platt, et al, 1964), of severely protein deficient pigs also demonstrated that endocrine glands were severely affected in protein calorie undernutrition.
Endocrine changes of the type outlined above could be expected to lead not only to fatty liver (Heard et al 1964), but also to changes in carbohydrate metabolism. Among the earliest observations made on pigs suffering from protein-calorie deficiency were: abnormally high levels of liver glycogen (Heard et al 1953) abnormal glucose tolerance, and changes in the islet of Langerhans suggestive of insulin deficiency (Stewart and Heard 1959).

**PANCREAS**

It was shown repeatedly by a number of observers that chronic restriction of dietary protein leads to impaired glucose tolerance in a variety of animals like the pig and the dog. Such impaired glucose tolerance may result from relative deficiency of insulin or from excessive antagonism or resistance to the action of insulin. The former seems to be characteristic of severe protein calorie deficiency, the latter of marginal protein calorie deficiency (Heard et al, 1964, Heard, Turner & Platt, 1964).

According to the evidence reviewed by Haist (1944), during starvation, whether due to a complete absence of food or a reduced intake of a balance diet, there is a reduction in the insulin content of the pancreas.
Rats starved for 48 hours showed a decline in basal serum insulin level from 26 ± 6 to 9 ± 2 μ units per ml. The insulin response to a glucose load by mouth was barely detectable and they showed persistent hyperglycemia. Insulin response to injected glucose also was less in starved rats. Response was restored completely after refeeding for 24 hours (Grey 1970). Other workers also reported decrease in serum insulin level in starved rats (Malaisse 1967; Szepsi 1971), rabbits (Yokoh et al 1968) and in pigs (Kenneth, R). After 48 hours of fasting, pancreatic tissue showed a gradual degree of cytolysis, with increasing hours of fasting, mitochondria were rarely seen, cell volume decreased but zymogen granules were still numerous (Paradasi 1964).

In the protein-calorie deficient pigs, the islet cells are crowded together, counts showed that the number of cells per unit volume is increased because the size of the individual cells is reduced (Heard et al, 1958). Halder (1962) tube-fed a protein free diet to rats for 6 days and found a reduction in size of the individual islet cells and loss of aldehyde-fuschin positive granules in most of the cells. In contrast to this degranulation within the islets, there are in the protein-deficient pigs single cells, scattered among the atrophied acinar cells, which contain aldehyde fuschin-positive material.
Selective phloamin staining of the alpha cells (Gomori, 1941) indicated that the ratio beta:alpha cells was low in deficient pigs (Stewart & Heard 1959, 1960). The results of a few counts of the islet cells of young pigs suggest that, as in the rat (Mosca, 1956; Hellman, 1959) the ratio of \( \beta/\alpha \) cells was lower in young animals than in adults and it seemed likely that the \( \beta/\alpha \) cell ratio found in the protein-calorie deficient pigs was further evidence of immaturity being similar to the continuation of the immature distribution in rats hypophysectomized at about 32 days of age (Mosca, 1957). Few other reports describing the effect of diet on alpha and beta cells are available. Rats fed a diet of starch, sugar, fat and minerals (Verne and Herbert, 1953) suffered a severe loss of pancreatic alpha cells.

At post mortem the islets of Langerhans show reduced cells size, degranulation of \( \beta \) cells, and a low \( \beta/\alpha \) cell ratio (Stewart et al., 1959; Stewart et al. 1960; Syoboda 1966; Platt 1967). The glucose tolerance was impaired in life and sensitivity to insulin was however, increased.

Malnourished dogs and pups malnourished from birth showed crowding of nuclei and reduced size of islet cells, sometimes to a severe degree. Changes in the \( \beta/\alpha \) cell ratio were less than in the pigs. Extensive
degranulation of the islet cells was seen in pups malnourished from birth; these pups died before they were 6 weeks old.
The state of activity of the thyroid gland is revealed by the shape of the follicular cells (Goormaghtigh and Thomas, 1934), the concentration of colloid-like droplets within the cells (De Robertis, 1942), the number of colloid vacuoles (Aron, 1930), and the staining reactions of the colloid.

In rats, during chronic starvation the thyroid gland atrophies (Jackson, 1915; Nikitin, 1962). In addition to the reduced weight of the thyroid gland there were vacuolization of the cytoplasm, granular degeneration and hyperchromic and pyknotic nuclei. In pigs, on protein deficient diet, Platt and his colleagues (Platt, 1962; Platt & Stewart, 1962; Stewart and Heard, 1960) observed that the follicular cells were flattened, there were very few droplets in the cytoplasm, the colloid was eosinophilic and the Aron vacuoles were few. Protein-calorie deficient rats also show striking evidence of reduced activity (Ramalingswami, 1965). When rats were tube-fed on a non-protein diet for 6 days only, no morphological change was observed (Halder & Platt, 1962) but when they were kept on a low caloric diet for one year, changes similar to those in the pigs were found (Nikitin, 1962). Rats on protein poor diets had a reduced rate of hormone synthesis (Volkov, 1971).
This change in thyroid in protein deficient pigs, might also contribute to impaired glucose tolerance (Kusama, 1957; Scow, et al., 1954; Macho, 1960), but reduced thyroid function is probably of greater importance as indicative of atrophic changes in the hypophysis. Conversely, it has been reported that on "recovery" the thyroid glands of pigs previously fed on protein deficient diet appear "similar to glands which have been stimulated by thyrotropin" (Platt, Heard and Stewart, 1964). Atrophy of the hypophysis in severe protein-calorie deficiency suggests diminished growth hormone production. The consequence of growth hormone deficiency might be expected to include prolonged hypoglycemia following insulin administration and the eventual fall of blood sugar concentration to hypoglycemic levels following intravenous glucose (De Bodo, 1958). Both these signs were regularly observed in the severely protein-calorie deficient pigs. In deficient pigs values for sensitivity to insulin is lower than normal.

Thyroid glands from puppies malnourished from birth were immature, the colloid content was low, cells were often found within the colloid vesicles which are irregular in shape and size, and there were large areas of intervesicular cells (Cooper, 1925). Glands from dogs born of normal mothers and then maintained on low protein diets were similarly, but less severely,
affected than were those of malnourished pigs.

**PITUITARY**

In rats, subjected to chronic starvation, there was a pituitary weight loss of 25% as compared to a total body weight loss of 36% (Jackson, 1915). The parenchymal cells of the pituitary underwent a decrease in size; the nuclei were hyperchromatic and mitoses were depressed. The reduction in cell size was principally due to a loss of cytoplasm which stained poorly as a result of which strongly chromophilic cells became weakly chromophilic and even chromophobic. After a few weeks of refeeding, the hypophysis became normal for most part of the gland, although more or less atrophic areas might persist for indefinite periods. Mulinos & Pomerantz (1940), also observed that the pituitary gland underwent weight loss (34%) in chronic starvation in adult rats; the parenchymatous tissue likewise showed atrophic changes.

Abnormalities in the pars anterior of protein-calorie deficient pigs (Godwin & Platt, 1960) included vacuolation of the cells and loss of cytoplasm. The reduced cell size resulted in a crowding together of nuclei, which were often hyperchromatic, and the identification of different cell types became difficult owing to the reduction of the cytoplasmic granules. In the
most severely affected animals areas of necrosis and small cysts lined with ciliated epithelium could be seen.

Similar changes were found in the hypophyses of malnourished dogs and puppies, malnourished from birth; the reduction in cell size and hyperchromasia of the nuclei being particularly prominent.

The consumption of food of inadequate quantity and/or quality has long been recognized as leading to atrophic changes in the hypophysis (Jackson, 1925). And it was suggested that many changes in growth, maturation of protein-calorie deficient subjects could be related to reduced activity of the hypophysis (Mulinos and Pomerantz, 1940; Schwartz et al, 1951; Srebnik and Nelson, 1962). Rats maintained on protein free diets showed a decrease of the total amounts of all the hormones, Follicle-stimulating hormone, interstitial cell-stimulating hormone, growth hormone, thyrotropic hormone, in the younger of the deficient groups although the reduction in TSH was small. The thyrotropic hormone was not affected in the older group; the other hormones tested were reduced but less severely than in the younger animals.
In the adult rat, chronic starvation may be attended by a loss of about 33% of the body weight. The brunt of the weight loss is borne by the subcutaneous fat and muscle, but the weight of the adrenal gland was also shown to undergo a 10% decrease in weight (Jackson, 1915). There were also histological changes in the outer and middle zones of the cortex but inner zone appeared normal. The cell size was reduced about 20% in the middle zone; the decrease was probably due to loss of cytoplasm; pycnotic nuclei were also present (Jackson, 1919). Similarly progressive atrophy of adrenal glands was reported by Mulinos and Pomerantz (1941); the atrophy was more marked in females than in males. But if there were some added stresses over and above the undernutrition, like injection of foreign materials, some other concomitant disease and even administration of drugs, prevented the decrease in weight of the adrenal glands. Such normal sized glands also resulted if pituitary from normal rats were grafted to chronically starved rats. It, therefore, appeared probable, that in such rats the production of adrenocorticotrophic hormone was decreased and the atrophy of the adrenal glands was a secondary phenomenon. Cameron and Carmichel (1946) failed to demonstrate any change in the adrenal glands of rats, who were subjected to chronic starvation.
In acute starvation, however, the adrenal glands reported to be hypertrophied (Vincent & Hollenberg, 1920). The hypertrophy was the result of an increase in the water content of the cells; the dry weight of the adrenal gland was not increased (Cameron & Carmichael 1946). In experimental animals, subjected to protein-calorie deficiency, the changes in the adrenal glands were less consistent that in the other organs. For example McCarrison (1921) concluded that the "functional perfection of the adrenal glands is dependent on the quality of food". In rats kept on a protein-deficient diet, the adrenal glands were large in proportion to actual body weight (Leathem, 1958). In contrast, Munro et al (1962) reported that in adult rats, kept on a protein free diet for 5-11 days, there was a greater reduction in the weight of the adrenal glands than that of the whole body.

In pigs exposed to protein calorie deficiency, the secretory activity of the adrenal cortex was less impaired than that of the other endocrine organs. Histological evidence showed no lack of adrenalin secretion in severely protein-calorie deficient pigs (Platt et al, 1964) and in these animals, injected adrenalin raised the blood sugar concentration well above the normal fasting level. The liver phosphorylase system therefore presumably remained intact. Adrenalin was, however, ineffective in correcting profound hypoglycemia.
In the protein-calorie deficient pigs absolute excretion of 17-OHCS was lower than normal; so also was the size of the animals. When results were expressed in terms of body weight it was seen that protein-calorie deficiency did not result in diminished excretion of 17-OHCS; on the contrary raised excretion rates were found in most of the marasmic animals. This is in agreement with the results with children (Castellanos & Arroyave, 1961), as also is the fact that ACTH produced an increased excretion of 17-OHCS from pigs (receiving low protein and high carbohydrate diet, and not from pigs receiving low protein, low caloric diets representing Kwashiorkor and marasmus respectively. Excretion of free 17-Ketosteroids was diminished both absolutely and relatively to body weight in all the severely protein-calorie deficient animals.

Signs of hyperadrenocorticalism (Frawley et al. 1959) which were also characteristic of severe protein-calorie deficiency include: impaired glucose tolerance without ketosis; accumulation of glycogen in the liver; sodium retention with mild potassium depletion; increased serum pyruvate and lactate levels; involution of the thymus and osteoporosis.
Relative hyperactivity of the adrenal cortex is not necessarily inconsistent with insulin sensitivity and failure to raise blood glucose levels following insulin hypoglycemia. These phenomena had been shown to occur in severely protein-calorie deficient pigs and humans (Cooke et al, 1964). The explanation probably lay in reduced growth hormone production, for De Bodo and Altszuler (1958) have demonstrated that in the hypophysectomized dog, adrenocortical hormones were much less effective than growth hormone in eliminating insulin hypersensitivity.

All the available evidence points to the conclusion that severe protein-calorie deficiency leads to changes in the endocrine glands. Severe shortage of calories leads to maximal production of ACTH and of adrenocortical hormones, but not necessarily to marked changes in the secretion of other endocrine glands (as in pigs fed low protein, low calorie diets and in marasmic children). Severe shortage of protein accompanied by a relatively adequate intake of calories leads to severe deficiency of insulin and of thyroid and growth hormones without affecting adrenocortical activity (as in pigs fed the low protein diet and in marasmic kwashiorkor); extra carbohydrate intensifies these effects (as in pigs fed the low protein, high carbohydrate diets and in children.
suffering from kwashiorkor). It has been claimed that endocrine changes of this nature account for the fatty liver and many other abnormalities of kwashiorkor. In particular they help explain the impaired glucose tolerance, insulin sensitivity and hyperglycemia, and excessive storage of glycogen in the liver.
Digestion and Absorption of Carbohydrate

Carbohydrate metabolism has not been as extensively studied as protein metabolism in human subjects. It was shown that in human beings, subjected to total carbohydrate deprivation for 28 days, there was a reduction in disaccharidase activity of the small intestine as early as 3 days after the start of the fast, and in alkaline phosphatase activity after 14 days. These changes were accompanied by significant alterations in the histology of the mucosa, as revealed by light microscopy (Knudsen et al., 1968).

The absence of any detectable changes in histology confirmed the observations in experimental animals that fasting does not result in mucosal atrophy (Brown et al., 1963). No special vulnerability of intestinal lactase activity to the effect of fasting was noted, as has been suggested to occur in disease states associated with abnormal small intestinal histology (Stanfield, 1965; Shmerling, 1964). In another study it was shown that complete lactose deprivation for 42 days was not associated with a significant change in lactase activity or in lactose tolerance in human subjects. (Knudsen et al., unpublished data).
On refeeding with carbohydrate, there resulted a significant increase in intestinal protein content and in the activities of sucrase, maltase and alkaline phosphatase. Refeeding with fat had no significant influence on any of the parameters measured (Knudsen et al., 1966).

Gastrointestinal symptoms, especially chronic diarrhoea were common among patients suffering from protein-calorie undernutrition. (Obeysekere, 1966; Moglinicki, 1953; Schnitker, 1951). Davies (1948, 1952) described a selective atrophy of exocrine glands of the pancreas, small intestine, salivary and lachrymal glands. Dietetic factors especially protein malnutrition can produce pancreatic damage (Ramalingswami, 1964; Carazutti, 1966). Considerable amount of experimental evidence exists on the effect of protein malnutrition and amino acid deficiencies on the synthesis of pancreatic enzymes (Wang & Grossman, 1951; Magase and Hong, 1956; Lyman & Wilcox, 1963).

The fundamental histological abnormality in the pancreas in protein-calorie malnutrition is atrophy of acinar cells associated with marked diminution of secretory granules, and eventually fibrosis of the gland with sparing of islet cells (Veghelyi, 1950; Thompson & Trowell, 1952; Suzanne, 1967; Davies, 1948; Blackburn, 1969; Scrimshaw, 1961). Significant association between
malnutrition and pancreatic calcification in adults has been well described in many tropical countries (Zuidema, 1959; Kinners, 1963; Banwell, 1967). Autopsy studies in children and young adults who have had protein-calorie malnutrition and were untreated or inadequately treated showed chronic pancreatitis with fibrosis and acinar atrophy (Davies, 1948; Bras, et al, 1957). The characteristic alterations of exocrine pancreatic function in adult protein calorie malnutrition were reductions in enzyme and bicarbonate concentrations with preservations of a normal volume response (Jorge Palaez, 1966; Tandon, 1969). Tandon et al (1970) demonstrated that three months of dietary therapy resulted in considerable improvement in these abnormalities, with almost complete recovery of bicarbonate and lipase secretion and improved protease secretion. Amylase secretion, which initially was similar to that in the control subject, showed no increase following therapy.

It has been suggested that protein depletion leads to a deficiency of disaccharide splitting enzymes in the gut and that this is a significant factor in causing diarrhoea (Bowie et al, 1963). Several papers were published presenting case histories of adult patients with proved isolated deficits of intestinal mucosal disaccharidases, in most instances associated with diarrhoea. The presumption of an enzymatic deficit was furthered by
showing improvement with addition of the disaccharides to the diet or tolerance test (Dahlquist, 1963; Auricchio, 1963; Sonntag, 1964).

Atrophy of the intestinal villi is a feature commonly associated with kwashiorkor (Trowell et al, 1954; Brock, 1961, Stanfeld et al, 1965). In experimentally induced protein malnutrition in primates, well marked changes in the function and structure of the small intestine have been reported (Dep and Ramalingswami, 1964). While the syndrome in children has attracted widespread attention, the problem of protein malnutrition in the adult population has received very little attention (Obeysekere, 1966). Adult patients whose main presenting features were oedema, hypoproteinaemia and a dietary history of deficient intake of protein also showed diarrhoea. They showed intestinal absorption defects like the children. They also had a alterations in the intestinal mucosa in the form of blunting of villi, fusion at their bases, and variable inflammatory cell infiltration of lamina propria (Zandon et al, 1968), and the entire picture are reversible by high protein diet. It is well known that the epithelial cells lining the intestinal villi have a high rate of turnover and require building material in the form of protein to replace the shed cells (Crosby, 1961). So in protein deficiency these cells should be susceptible. Mayoral et al, 1967.
reported functional and structural changes of the small bowel with malabsorption due to protein malnutrition. Holmes (1959) also recorded less absorption in protein deficient group. Deo and Ramalingaswami (1964) had found similar changes in the structure and function of the small bowel in experimental protein deficiency in rhesus macaque monkeys.

Although vaguely suggested by several authors (Sheehy & Floch, 1964), and confirmed in children by others (Stanfield, 1965; Burman, 1963; Dean et al. 1963), the possible causation of a malabsorption syndrome by protein-calorie undernutrition was mentioned only in Zubiran's paper (1961). Experimental evidence that protein deficiency caused intestinal damage was reported in pigs by Platt et al. (1964) in rats by Takanto, (1964) and in rhesus monkey by Deo and Ramalingaswami (1964). Severe protein malnutrition is capable of producing a clinically biochemically and histologically definable, mild to moderate malabsorption syndrome in adults (Meyoral et al. 1967). The malabsorption syndrome encountered was completely non-specific in its characteristics, but different from any other previously described condition in its behaviour with a therapy consisting simply of a diet adequate in protein content.
BLOOD SUGAR

From an extensive study of diabetic patients, Allen (1913) came to the following conclusion: "Reduction of blood-sugar below the normal lower limits is a difficult and unusual matter in the normal organism. Approximately the normal percentage is stubbornly maintained through prolonged starvation, almost up to death." Less than 10 years later, Weeks et al. (1923) found the situation in human beings to be otherwise. In some of their epileptic patients starved for 3 weeks, the blood sugar levels decreased in the first week and then increased. A more complete study of the changes in the blood constituents was made by Lennox, O'Connor and Bellinger (1926) on patients who were fasted as a therapeutic measure for the relief of convulsions. In most of these cases, the blood sugar decreased during the first week and then rose nearly to its pre-fasting level. Shope (1927) determined the serum sugar concentration in normal young woman without food for 5 days. The level decreased from a control value of 110 mg to 37 mg on the fourth day and then increased to 68 mg on the last day.

However, when the preceding diet was of average composition, human beings as well as most other animals show an initial decrease in the blood sugar level followed by a gradual return to normal. This general
trend was confirmed for adults by Slotopolsky's study (1932). If the diets used before the fast were high in fat or protein the blood sugar levels were maintained close to control values during the abstinence from food.

Joslin (1923) apparently was the first to note the change in the blood sugar level of human beings during experimental semi-starvation. In his study a healthy young woman stayed without food for 4 days and then began eating again starting with very small amounts of bouillon. The blood sugar level decreased from a control value of 120 mg per 100 cc of blood to 80 mg on the eighth day of the experiment, when the food consumed by the subject was 240 calories per day. There was considerable interest in the blood sugar levels of the edematous patients (hunger edema) seen during World War I. All the reports agree that there was very little if any change in this constituent even among the cases with severe edema, Knack and Neumann (1917) presented the largest number of cases in which the blood sugar was determined by Bang's method (1913) both during and after the disappearance of edema. The mean value for the blood sugar in the people with edema was 97 mg per 100 cc of blood, which increased to 106 mg after normal food consumption was resumed. The degree of oedema had no influence on either the initial or the final blood sugar levels.
During World War II some of the reports on semi-starvation indicated relatively normal blood sugar levels. Leyton (1946) determined, by means of the Folin-Wu technique (1920), the blood sugar levels in 153 Russians who were interned in Germany. These values ranged from 69 to 100 mg per 100 cc of blood, with an average of 81 mg. This is just below the recognised range (90-120) accepted for this method (Hawk et al., 1947).

In contrast to the above are the reports from France, Belgium and Poland. These made frequent reference to the occurrence of a hypoglycemia which appeared to be so severe that it was described as hypoglycemic shock.

The work of the French investigators in this field has been reviewed at some length by Gounelle and Marche (1946). Apparently hypoglycemia was not limited to institutionalized individuals. Some of the first cases were seen among civilian laborers (Barbier and Piquet, 1943), but the largest number of cases were seen in mental institutions and prisons where the food supply was most restricted. Coma developed in some cases very rapidly.

There are reports of a similar condition among the inhabitants of Brussels (Basterie, 1947) who, like the French patients, went on to death in spite of intravenous glucose injections.
Among the men rescued from the German concentration camps who were studied at Mainau in 1945, the blood sugar was examined in 26 individuals by Lamy, Lamotte and Lamotte - Barrillon (1948). The blood sugar level had a low value.

In persons who were almost equally emaciated and who were still actively starving in Warsaw in 1942, much more consistent and profound hypoglycemia was found (Fliederbaum et al, 1946).

Burger, Sandstead, and Drummond (1945), with the nutrition survey teams that went into Holland after the liberation from German occupation, reported that some individuals were suffering from psychosis, which was attributed primarily "to hypoglycemia and responded well to intravenous glucose". Another report on the development of hypoglycemia among semi-starved individuals was that by Musselman (1945). The American soldiers who were captured by the Japanese on the Philippine Islands were reported as showing symptoms of hypoglycemia when the food supplies were reduced to 1000cal or less per day.

The French workers (Gounelle et al, 1943; Bachet, 1943a; Gounelle and Marche, 1946) suggested that many of the sudden deaths occurring among the edema cases during World War I actually were due to hypoglycemic shock.
Blood sugar values as low or lower than any of those reported from starvation hypoglycemic shock have come out of India. During the Bengal famine of 1943 Chakrabarty (1947a) made blood sugar determinations on 407 severely starved patients. The \textit{maxim} values ranged from 19 to 307 mg per 100 cc, with an average of 76.7. In 5.6 per cent of the cases the values were below 40 mg per cent. As these patients recovered from starvation their blood sugar levels gradually increased (Chakrabarty, 1947b). Again, as mentioned by Bose, De, and Mukherjee (1946) and by Fliederbaum et al (1946), the clinical symptoms associated with this extreme hypoglycemia were not comparable to those seen in insulin shock at similar blood sugar levels.

Obeyesekere (1966) found that the level of fasting blood sugar was invariably low and averaged 68 mg per 100 ml (range, 45 to 82 mg per 100 ml in Forty patients) in malnourished Ceylonese adults. Several other workers also reported similar findings in protein deficient adults (Zubiran and Gomez-Mont, 1953; Trowell & Holmes, 1948; Gillman and Gillman, 1951).
In a study of patients with hepatic disease, Traugott (1922) noted a marked hypoglycemia following relatively small doses of glucose. The great variation in his control glucose tolerances, made on apparently healthy subjects, convinced him that the nutritional condition might explain some of his individual variability. To test this, he reduced his own food intake by one half for 5 days and then for an additional 3 days went completely without food. The increase in his blood sugar level following glucose was much greater after the starvation period than before. Sevringhaus (1925) observed the same thing after 2 days of starvation.

Sweeney (1927) found that when medical students fasted for 2 days, the subsequent glucose tolerance was similar to that secured following a 2-day high fat regimen. Because of the high fat diet of the Eskimos, Heinbecker (1928) studied their glucose tolerance curves both before and after 62 hours of fasting. The basal blood sugar during the starvation decreased from 110-120 mg per 100 ml to about 80 mg. The glucose tolerance after the ingestion of 20 mg 2 gm of glucose per kg of body weight were normal in the control period. After 3 and a half days of starvation the glucose tolerance showed blood sugar levels close to 300 mg per 100 cc. These returned only very slowly to normal. Sugar appeared in the urine approximately 2 hours after the glucose dose and in 2 cases stayed there for 10 hours.
As far as the blood constituents are concerned, Wollenberger and Linton (1947) probably made the most thorough study of the changes resulting from the ingestion of a dose of glucose. Their glucose tolerances were made on normal young men who had been without food for 7 days. In comparison to their control period curve, starvation produced a marked increase in the highest blood sugar level attained together with a considerable delay in the time at which the peak appeared. They also followed the blood pyruvate and lactate levels, which in normal subjects closely paralleled the changes in blood sugar. After the starvation period, however, the peak in the pyruvate and lactate curves occurred about an hour after the maximum blood sugar level.

Glucose tolerances in acute starvation were associated with a gradual decrease in the blood inorganic phosphate, (Wollenberger and Linton, 1947) a decrease in the phosphorylating mechanism (Kaplan and Greenberg, 1944) and the development of starvation ketosis (Sevringhaus, 1925; Cori & Cori, 1927a; 1927b). Inusuka (1971) reported that glucose tolerance in fasting subjects were decreased. Bell (1972) also showed marked decline in glucose assimilation constant (kg) seen in non-obese subjects (on a 10 day fast), the mean Kg. value was not significantly changed.
The great variety in the types of curves on may secure for glucose tolerance studies on semi-starvation subjects is best illustrated in the work of Bose, De and Mukherjee (1946) with starvation cases admitted to the hospital in Calcutta during Bengal famine of 1943. The group was divided into the severely edematous cases and those who were extremely emaciated with no signs of edema. Twelve of the patients with oedema showed no change in the blood sugar concentration during the 3 hours following the ingestion of 50 or 100 gm of glucose. In another 16 cases, the blood sugar never showed any increase, but after an hour and a half it started to fall and by the third hour reached values as low as 40 mg per 100 cc. Both sets of glucose tolerance curves were probably affected by disturbances in absorption since when 0.2 gm of glucose per kg of body weight were given intravenously, a marked peak occurred in the blood sugar levels.

"These were cases of chronic malnutrition due to starvation for prolonged periods. Their histories revealed that, owing to poverty, they were already on an insufficient diet prior to actual starvation" (Bose et al, 1946). A severe restriction of food occurred from 6 weeks to 3 months preceding their hospital admission, when it was found that most of them had pneumonia, malaria, and dysentry.
At Warsaw, sugar tolerance tests, using 50 gm of glucose by mouth in adults, were made on 45 persons who had been subjected to prolonged semi-starvation but had not been totally deprived of food. The response of the blood sugar was very weak and much delayed in appearance; maximum values of 80 to 90 mg per 100 cc appeared after 2 hours or more, and this was often followed by a profound decline to a value of the order of half of the initial (fasting) level (Fliederbaum et al 1946). The low point of post-glucose hypoglycemia sometimes only 20 to 25 mg, was usually 4 or more hours after ingestion of the sugar; the previous fasting level was generally not regained for another hour or more.

In a brief note on studies made during the Bengal famine, Chakrabarty (1947a) reported that the blood sugar level after 50 gm of glucose showed a gradual rise for about 4 hours; in normal individuals the highest rise occurred within one hour and the level returned to normal within two hours. Again, many of the subjects undoubtedly suffered from acute starvation. Chakrabarty (1947a) mentioned that microscopic examination of material secured at autopsy showed extensive epithelial denudation and submucous hemorrhage in the small intestine which might have interfered with the absorption of sugar. During recovery the glucose tolerance
tests were repeated at 2 week intervals. As the body weight increased, the subjects showed a gradual elevation in the fasting blood sugar level. At the same time the glucose tolerance curve returned to normal in all respects (Chakrabarty, 1947b). Walters et al (1947a), reported somewhat similar results in starved Indian soldiers.

In France during the German occupation Gomelle et al (1942d), found extreme variations in blood sugar response following 50 gm of glucose similar to those observed by Bose, De and Mukherjee (1946). This varied from an abnormally high rise in blood sugar to no change.

There are few reports of tolerance tests on carefully controlled cases of semi-starvation. Perhaps the closest approach was the work of Malmros (1928). He restricted a normal young man to 1760 cal per day for 3 days. At the end of this period the blood sugar curve after ingestion of 62 gm of glucose was similar to that in the control period except that it returned to its base level more slowly.

Gillman and Gillman (1951) reported impaired tolerance to intravenous or oral glucose in severely malnourished African adults and some, like the pigs, showed a "paradoxial" curve in that blood glucose concentration
fell below the fasting level. Reports from several centres also showed that impaired glucose tolerance on severely malnourished African adults (Holmes & Trowell, 1948) Ceylonese adults (Obeysekere, 1966), malnourished patients in San Salvador, central America (Alvarez, 1972).
Glycogen

The biopsy study of liver samples (removed during operation for gastric or duodenal ulcer) shows an average liver glycogen content of 3.47g per 100 g of wet tissue and fell to 1.06g after fasting for 24 hours. Infusion of glucose raised the glycogen content (level) in fed and fasted patients by an equal amount (Sunzel, 1968).

Very little information is available on the glycogen stores of human beings during periods of semi-starvation. Schittenhelm & Schlecht (1918) found no microscopic evidence of any glycogen among German civilians who died from hunger edema during World War I.

Holmes & Trowell (1948), studied the glycogenolytic function of the liver in malnourished adults by means of serial liver biopsies. Glycogen determinations demonstrated the presence of appreciable quantities in the liver, the values ranging from 0.8 g to 4.8 gm per cent (15 patients). In 5 control patients liver glycogen increased within two hours after intravenous administration of glucose whereas in 8 malnourished individuals the ability on the part of the liver cells to store glycogen was diminished but not abolished (Cross & Holmes, 1937; Dawson & Holmes, 1939; Holmes & Lehman 1940).
Gl-6-Pase activity was decreased, and phosphogluco-
mutase activity increased in liver biopsy specimens
from the malnourished lactating women in comparison
with values for normal individuals (De Souza, 1959).
HORMONES IN CARBOHYDRATE METABOLISM

Pituitary

Data on the histological changes that occur in the pituitary gland of man during starvation are extremely limited. In the starved man reported by Meyers (1917) the anterior lobe of the pituitary was congested and hemorrhagic. The epithelium showed "great reduction and degeneration similar to that shown in the adrenals, and in some places (was) displaced by blood". Only a few masses of colloid were found, and the characteristic chromophile granulation was greatly reduced. Ublinger (1948), also found similar changes in inmates of German concentration and prisoner of War camps. He reported normal posterior pituitary in all cases. Lamy, Lamotte, and Lamotte-Barrillon (1946c, 1948) reported eosinophilia in the pituitary of 5 out of 17 cases of death from starvation.

Stein and Fenigsten (1946) found the intermediate lobe of the pituitary underdeveloped in all cases; brown pigment cells and free pigment were seen in 2 cases, and in 2 cases there were more acidophilic cells than basophilic cells in the anterior lobe. Ryss (1943), from his observations during the siege of Leningrad, also concluded that the clinical symptoms pointed to a disturbance of the function of hypophysis in starvation.
The pathology of the endocrine glands has been studied extensively by Zubiran and Gomez-Mont (1953) on subjects who died from malnutrition in Mexico. They found atrophy and degenerative changes of the anterior lobe of the pituitary gland, adrenal cortex, ovaries, testes and to a lesser extent, the thyroid gland. They likened the changes to those found in senility which represent a state of relative involution consistent with decreased functional activity. They further suggested that the type of changes in the ovaries, testes, adrenal and thyroid glands were similar to those observed in cases of early primary pituitary disease.

A microscopic examination was made of 101 glands of which 49 were found to be atrophic. Degenerative lesions in the anterior lobe were found which consisted of increase in vacuolization (41 cases), pycnosis (42 cases), cellular atrophy (19 cases) and calcification (6 cases). Different cell types were found in normal proportions in all except 12 cases, in which a moderate increase in eosinophilic cells were apparent. The stroma showed alterations in 52 cases, consisting more frequently of small scars but sometimes of large scars or of diffuse increase in connective tissue. Basophilic invasion of the posterior lobe was found in 39 cases; pigmentation of this lobe in 7 cases; and lymphoid cell foci in or around the intermediate zone in 6 cases.
In view of the lack of reliable tests of pituitary function, disturbances in the activity of the gland must be judged indirectly by the activity of its subordinate glands.

Although there were no specific anatomical lesions in the endocrine glands that corresponded to a diminished pituitary stimulus the type of changes found in ovaries, in the testicles, in the adrenals, and in the thyroid suggests an involution similar to that observed in cases of early primary pituitary disease (Perkins and Rynearson, 1952) and speaks in favour of a generally lowered pituitary activity. This diminished activity was not permanent, but responded rather easily to adequate food intake.

Adrenals

Meyers (1917) reported a 20 per cent decrease in the weight of the adrenals and a 36 per cent decrease in body weight in a man who ingested only water for 60 days prior to death. The atrophy of the zona glomerulosa was very marked, and many "shadowy cells" were seen in some portions of the glands. Meyers emphasized that these were not post mortem changes but undoubtedly had occurred as a result of the prolonged period of starvation. Enright (1920a) stated that among the starved Turkish prisoners of war with edema "the suprarenals of all....... were found to be atrophied". Pellegrini (1920) also found a small
decrease in the size of the adrenal glands of Italian prisoners of war who died from undernutrition.

The 200 war edema cases reported by Schittenhelm and Schlecht (1918) had the usual signs of starvation—loss of body fat, wasting of muscles, bradycardia, low blood pressure, anemia, and weakness. On autopsy the adrenals were found to be enlarged but normal in general appearance. Byrne (1919) and Kirieger (1921) observed an increase in the weight of the adrenals. Schlif (1922) concluded from a series of more than 2000 autopsies that there was no relation between the weight of the adrenal glands and nutritional status. Stein and Fenigstein (1946) reported a diminution of fat in the adrenals in nearly a half of the prisoners of war in Warsaw.

Uehlinger (1948) found only relatively small histological changes in the adrenals of famine cases. The medullary tissue was normal. The cortex in some cases showed hydropic swelling, partial or total fatty degeneration, increased spongocytes, and fibrosis of the capsule and zona glomerulosa. Partial cortical sclerosis was frequent. Partial fatty infiltration of the cortex was common but total infiltration was rare.

In the cases who died shortly after liberation, Lamy, Lamotte and Lamotte-Barrillon (1948) showed that there was depletion of lipids from the adrenals and in some
cases there was cellular atrophy. Babes and Jonesco (1906b) also found a low content of adrenal fat in human in starvation.

All these observations tend to show that unequivocal evidence for atrophic and degenerative changes in adrenal glands due to starvation acute or chronic does not exist in man.

Zubiran & Gomez-Mont (1953) made an extensive study of adrenals in malnourished adults in Mexico. A total of 126 glands were examined. On gross examination, 48% of these were smaller than normal and 63% showed lipid depletion. On microscopic examination thinning and irregularity of the cortex (15 cases), accessory cortical tissue and nodule formation (59 cases) were observed. The intracellular distribution of lipids was abnormal (77 cases); many had unusually large drops of lipid in the internal portion of the fasciculata and reticularis, and nearly all showed confluent lipids and cells resembling those of normal adipose tissue. Atrophy and excessive pigmentation of the reticularis were noted (26 cases). Foci of lymphoid cells were found in 100 cases, more frequently in medulla, but sometimes in both medulla and cortex.

The findings in general suggest atrophy of the cortex, although nodule formation and presence of accessory adrenal tissue were frequently found in a series of consecutive autopsies (Commons and Callaway, 1948).
Excretion of 17-Ketosteroids

Seventeen Ketosteroids excretion show an abnormally low value in 91% among 174 undernourished subjects. About a half of those people had reached normal values of excretion after treatment and in the other half only slight increases were found although the observations were prolonged as long as four months. The ability of the adrenals to respond to stimulation was studied by injection of ACTH and followed by an increase in 17-Ketosteroids excretion and by a normal decrease in eosinophile counts. This might indicate that the primary defect in function was in pituitary and not in the adrenals themselves. However, in no case did increase in 17-Ketosteroids reach a level such as would be expected from a normal adrenals. This, together with the anatomical lesions observed in the adrenals and the incomplete response to treatment, implies a definite participation of the glands themselves.

Thyroid

In persons suffering from war edema the thyroid gland normal weighed a as much as in normal persons (Oberndorfer, 1918). The histology of the gland showed small follicles and a greatly diminished quantity of colloid, suggesting a greatly decreased secretory activity. Meyers (1917) described in case of starvation the epithelium of the acini
was often hardly recognizable. Area of diminished colloid were present, but most of the gland was converted into a mass of colloid with distended acini. The thyroid weight was not recorded but "the picture is that of atrophy ( and ) exhaustion". But Uehlinger (1948) and Stein and Fenigstein (1946) found no morphological change in the thyroid gland. This led Uehlinger (1948) to conclude that the decrease in BMR in famine-stricken persons are independent of thyroid changes.

Of a total of 131 glands examined by Zubiran and Gomez-Mont, 64 were small or frankly atropic. Many showed increased consistency and a few were grossly nodular. On microscopic examination, frequent and sometimes extreme variations in the size of individual follicles (73 cases), degenerative changes of the colloid (79 cases) consisting of sporadic or diffuse basophilia (55 cases), increase in vacuolization (34 cases), granular opacity (43 cases), or pigmentation (14 cases) were noted. The stroma was increased (61 cases), more often discretely but sometimes coarsely with partial hyalinization. Nodules were found in 14 cases, although these changes indicate lower thyroid activity they were found in younger individuals and cannot be attributed to age. Atropic lesions of the thyroid have been reported in malnutrition (Keys et al, 1950; Gillman & Gillman, 1951).
A slight decrease in protein-bound iodine (Starr et al, 1950) a normal level (Werner, et al 1949; Keating et al, 1950), and slightly decreased radioactive iodine uptake (Means 1951) have been reported in sporadic cases of malnutrition.
PANCREAS

The weight of the pancreas in Meyers* (1917) starved man was reduced 49 per cent while the body weight loss was 41%. The islet cells were small and degenerate and were difficult to recognize. All that remained of the islands was a fused mass of degenerated cells. While some of the cells were fairly well preserved, all were small and shrunk, away from the surrounding connective tissue. Krieger (1921) found the loss in pancreas weight during various chronic diseases with emaciation to be in conformity with the body weight loss. The glands were generally small, firm and anemic. Roessel (1919) observed no consistency in the loss of weight of the pancreas in his large group of autopsies on soldiers who died from chronic emaciating diseases. Schittenhelm and Schlecht (1918) and Bigland (1920b) reported normal exocrine tissue of the pancreas in war edema. In the victims of the Russian famine of 1921-22 the weight of the pancreas was only 10 to 20 per cent below normal. The islets were sharply defined and appeared relatively hypertrophic (Nicolaeff, 1923). In adults dying of malnutrition and tuberculosis, Smeden (1946) reported changes in the islet cells. "In the islets there was a moderate to marked diminution in the number of cells. Those still remaining stained indistinctly and had pycnotic nuclei. Between the cells there were spaces in which no stainable material was present. The cytoplasm was small in volume and homogenous and cedematous in appearance".
The victims of the Madras famine of 1877-78 had pancreas glands that were reduced in weight by about 40 per cent. The loss in weight of the pancreas was less in the female.

Chakravarty (1946), found that the islet cells were fewer in number than normal and foamy in structure in cases dying of famine in India. Some of them had extreme hypoglycemia and sugar tolerance was found to be bizarre in some of these cases (Mazumder & Mukherjee 1951).

Sukkar et al (1967, 1963) demonstrated a decrease in the levels of plasma insulin and growth hormone during a 6 hour fast, and insulin levels fell throughout the fast. After ingestion of protein both the concentration of insulin and growth hormone increased. Hunter (1968) and Adibi (1970) also reported a decrease of insulin during fasting. Yalow and Barson described low insulin levels in adults after prolonged fasting (1965).

Insulin tolerance on malnourished adults had low hypoglycemic indices (Obeysekere 1966).
CARBOHYDRATE METABOLISM IN PROTEIN CALORIE
UNDERNUTRITION IN CHILDREN.

Chronic diarrhoea constitutes a major part of the diseases of childhood. In those areas of the world where malnutrition is prevalent, infantile diarrhoea presents a major pediatric and public health problem. A large percentage of infants and children presenting at hospitals with diarrhoeas have evidence of malnutrition (Moodie, 1960; Bowie, 1960; Kahn, 1961; Truswell, 1963). Diarrhoea is said to be constantly associated with severe protein-calorie malnutrition (Trowell, 1958; Scrimshaw, 1955; Dean, 1957). It was considered that the diarrhoea was entirely due to gastrointestinal infection; it was also predominantly related to the pathologic changes of malnutrition (Burgess, 1961). Glucose and galactose malabsorption has already been reported (Eggermont, 1966; James, 1968) in infantile malnutrition. Schneider et al (1966) showed with autoradiographic technique that the lesion is localised in the epithelial cells of the small intestine. Autopsy (Passmore, 1957; Trowell, 1954, Jelliffe, 1955; Brock, 1961) and more recently biopsy studies (Stanfield, 1965; Burman, 1965; Berkel, 1970), have shown non-specific small bowel mucosal change.

These mainly involve villous fusion, broadening and atrophy with increase in cells of the lamina propria, and decreased height of the epithelial cells (Stanfield, 1965).
Electron microscopy examination reveals the presence of many lipid droplets in the cytoplasm of the jejunal absorptive cells. Golgi vacuoles were not distended with fat particles, and chylomicrons were markedly decreased in the intracellular spaces and lamina propia (Theron, 1971). The mitotic index is significantly lower in kwashiorkor than in the controls although not as low as in marasmus (Brunser, 1968). Diminished xylose absorption, steatorrhoea, and duodenal and jejunal atrophy on peroral biopsy have been demonstrated in malnutrition (Zubiran, 1961). Duodenal enzyme activity is diminished in the untreated case as compared to some normal figures (Burgess, 1964). Carbohydrate intolerance owing to congenital absence of disaccharide splitting enzymes is a newly recognised entity (Holzel, 1959; Weifers, 1961). In many cases of kwashiorkor no recognized intestinal pathogen is isolated (Coetzee, 1956; Scrimshaw, 1956) but it has been suggested that disturbance or overgrowth of intestinal bacterial flora (Smythe, 1958) may play a part in the etiology. Nitrogen (Hansen, 1960) and fat absorption (Holemans, 1955) have been shown to be impaired.

Studies in Cape Town have shown that in the majority of cases of local kwashiorkor the diarrhoea is fermentative and probably due to an acquired malabsorption of disaccharide (Bowie, 1965; Bowie, 1963). Fermentative diarrhoeas may be due to malabsorption of mono-di-or polysaccharides (Weifers, 1963; Weifers, 1961; Weifers,
In these children the monosaccharides appear to be absorbed efficiently although there is evidence that there may be some delay in absorption. Lactose malabsorption occurred in 65% of the cases and the malabsorption was found not to be transient (Bowie, 1967). Dean originally suggested that the lactose of milk was the cause of the severe diarrhoea found in advanced cases of protein-calorie malnutrition. He further showed that this diarrhoea could be controlled by reducing the amount of lactose present in the food. The malabsorption of lactose is due to diminished or absent lactase activity and this is presumably an acquired deficit secondary to the mucosal damage that occurs in malnutrition. No evidence was found of malabsorption of other disaccharides (Sucrose and maltose) although diminished sucrase activities were found in some patients. Most children with protein calorie malnutrition have a malabsorption syndrome. The malabsorption syndrome of malnutrition has been previously documented (Thompson, 1952; Gomez, 1954) and is probably due to a combination of hepatic pancreatic and small intestinal malfunction.

Although reduction of digestive enzymes has been blamed for gastrointestinal disturbances associated with malnutrition (Davidson & Passmore, 1966), the poor pancreatic enzyme output in patients with protein-calorie malnutrition was associated with significant absorption of nitrogen and fat (Hansen et al, 1960; Waterlow, 1960;
Gomez et al., 1957), Previous workers demonstrated that pancreatic enzymes could adapt themselves according to the predominant constituent of the diet (Grossman et al., 1942-43; Howard and Yudkin, 1963). But, all the children with kwashiorkor, who existed largely on a carbohydrate diet, had a deficient amylase output. This was a result of their poor intake of protein, which was essential for enzymes synthesis by the pancreas (Wachstein, 1954). Control children had a high amylase content.

In starvation the amylase activity in the duodenal juice from infants under 6 months of age was low, and lipase activity was lower in infants and children under 2 years of age than from children over 2 years (Ingomer & Tersler, 1967).

In 1925 Jackson (1925) described the atrophy and degranulation of pancreatic acinar cells that resulted from inanition. These pathological changes in the pancreas were very striking in infants dying of kwashiorkor, and was recorded in several parts of the world (Waterlow, 1943; Davies 1948, Hartz, 1949). Less commonly and perhaps in the more chronic cases, the atrophy was accompanied by other changes like fatty infiltration, dilatation of ducts with retention of colloid, and even diffuse fibrosis (Bras et al., 1954; Bras et al., 1956; Veghelyi, 1950). Histological studies showed that pancreatic ducts were spread in acute kwashiorkor (Trowell, 1954; Davies, 1948) but that the acini were constantly affected.
These pathological lesions in pancreas were also accompanied by functional changes. Yeghelyi (1943, 1950) studied 109 children during the siege of Budapest in World War II, when milk became unavailable. Within about 3 weeks there was a fall in the enzyme activity of duodenal juice. First lipase and trypsin fell, and then amylase. These changes began before malnutrition was severe, before oedema occurred and before there was any evidence of liver damage. They could not be prevented by vegetable foods or vitamins, and responded only to milk. Similarly in Egypt Badr El-Din and Aboul Wafa (1957) found that in malnourished babies trypsin began to diminish at an early stage, before the development of edema or liver enlargement.

Observations of the same kind were soon available in kwashiorkor. Magalhase Carvalho, Schmidt and Pinto (1947) found low levels of trypsin and lipase in convalescent children in Brazil. Dricot et al (1954) in the Belgian Congo recorded reductions in lipase, but the trypsin activity was found to be normal. Two very detailed studies of this problem have been made by Thompson & Trowell (1952) in Uganda, and by Gomez and his colleagues in Mexico (1954). In Uganda the greatest reduction was in trypsin, in Mexico it was greatest in lipase.
Quite different results have been obtained by several workers in England and North America who have measured duodenal enzyme activity in malnourished infants. McDougall (1950) found normal activity in 18 malnourished babies, mostly less than 6 months old. Bates and James (1956) made a similar study in 8 babies who were about 30 per cent below weight. The duodenal trypsin activity was normal. Waterlow (1948) found a normal appearance of the acini of some infants dying of marasmus. However, more detailed studies by Bras and his colleagues in Jamaica (1954; Bras et al, 1956) have shown that the position is not so simple. Many marasmic babies at autopsy did show pancreatic change, which were much less common in control series of children dying from non-nutritional diseases.

Barbezat (1968) performed pancreatic function tests on patients with kwashiorkor and marasmus. The volume output from the pancreas and the pH of the juice was unaltered in malnutrition while the enzyme (amylase, lipase, trypsin, chymotrypsin and ribonuclease) activities were reduced. The mean enzyme output was lower in children with kwashiorkor than with marasmus, but there was a distinct overlap in the result of pancreatic function tests in these two groups.

The rapid histological improvement in the pancreas after protein repletion (Trowell, 1954; Bras, Waterlow and De Pass, 1957) correlated well with the restoration
of pancreatic function demonstrated during recovery from kwashiorkor (Gomes et al, 1954). Functional improvement occurred within 4 days of commencement of dietary therapy.

Pancreatic function in children with marasmus was reported to be normal in some patients and abnormal in others (Anderson, 1942; Bate & James, 1956; Kerpel Fronius, 1960; Maddock, Farber & Swachman, 1943). Damus (1970) observed an enzymatic deficit of lipase and amylase but a normal response in volume and bicarbonate in marasmic infants. Especially lipase activity was markedly reduced both before and after therapy (even after 30 days of intensive therapy) as was the response to pancreazym.

Thus it was shown that exocrine function of the pancreas is changed in malnutrition (Meghelyi, 1950; Thompson & Trowell, 1952; Gomez et al, 1954; Waterlow, 1959; Barbezat & Hansen, 1968; Altmann, 1953, Badr El-Din, 1957). Malnourished patients showed enzymatic deficit, but a normal response in volume and bicarbonate suggesting a sparing of the ductules which produce the fluid secretion and the bicarbonate in the pancreas (Grossman and Ivy, 1946; Janowitz and Dreiling, 1962). The low enzyme output indicated acinar dysfunction or damage. Children with fibrocystic disease of the pancreas did not respond in volume or enzyme output to secretion or
pancreozymin stimulations (Maddock et al, 1943; Gibbs, 1950) in this condition both the ducts and the acini were affected (Davies, 1948; Anderson, 1938).

Thus malnutrition seemed to affect the pancreas in a manner analogous to "primary pancreatic insufficiency" and is characterized by an acinar defect rather than a defect in duct function as in fibrocystic disease (Hadron et al, 1969) where both are affected (Davies, 1948; Anderson, 1938).
BLOOD SUGAR

It has been suggested by Peters and Van Slyke (1946) that infants develop hypoglycemia during starvation more rapidly than adults. This, however, is not borne out by the work on starved children. Such work indicates that the blood sugar changes in adults and children are similar. Mogwitz (1914) starved 3 infants for periods as long as 73 hours and found most of the values were considerably below the control level. Somewhat similar results were secured by Lindburg (1917), who during a 60 hours fast noted a fall of blood sugar from 125 to 60 mg per 100 ml of blood in the first 24 hours and remained there for the duration of the experiment. Individual variations were noted by Shaw and Moriarty (1924); some children maintained their blood sugar level for 3 days, whereas others showed a precipitous decrease to levels as low as 38 mg per 100 ml. Part of this variation in blood sugar levels has been attributed by Rumpf (1924), without evidence, to the nutritional condition of the child at the start of the fast. In view of the recent findings with starved adults and the marked variation secured in blood sugar levels when different analytical methods are used, it seems likely that age is of only minor consequence in the response of the blood sugar level to starvation.
Information on the blood sugar level in semi-starved children is limited largely to marasmic infants. Here, as in adults the fasting levels are lower than in normal infants (Tisdall et al, 1925; Wilson et al, 1928; Brown, 1924-25; Jaso, 1932) and in some cases may be as low as 50 mg per 100 ml of blood. Calculations of the rate of carbohydrate metabolism indicated that when the rate was referred to the ideal body weight, it was normal (Wilson et al, 1928). The injection of insulin into these infants produced no change in the rate of glucose oxidation. This led Wilson and his co-workers (1928) to conclude that there was no fundamental difference in the carbohydrate metabolism of marasmic and normal infants. As the nutritional condition of these children improved, the blood sugar returned to normal levels (Brown, 1924-25). In fact Brown was able to find a fairly good correlation between "the relative state of nutrition" and the fasting blood sugar when the latter was plotted against the body weight expressed as a percentage of the standard weight.

Several reports indicate that the child suffering from protein-calorie undernutrition cannot metabolise glucose at the normal rate. Hypoglycemia in infantile malnutrition was reported as far back as the classical
period of German Pediatrics preceding World War I (Gobliner, 1931). Although Jaso in 1932 called attention to the prognostic significance of decreasing fasting blood sugar levels, Aballi (1950) in 1950 seems to be one of the first investigators to set the facts in their true light. Low fasting blood sugar in malnourished children has been reported from several centres (Tisdall, 1925; Chaudhuri, 1948; Holmes, 1948; Gomez et al, 1957; Baig & Edozien, 1965; Slone et al 1961; Whitehead, 1966; Hadden, 1967; Kerpel-Fronius, 1967; Oxman, 1968; Taltz, 1966) and hypoglycemia has been suspected as cause of death (Kahn & Wayburne, 1964). Bowie (1964) however, found normal levels with kwashiorkor. Rao (1965) working in India found also normal blood sugar levels in his cases of Kwashiorkor.

GLUCOSE TOLERANCE

There are very few studies on glucose tolerance in semi-starved children. Glucose tolerance tests were made on 8 marasmic infants who were less than 80 per cent of their expected weights; the blood sugar responses were within normal limits (Brown, 1924-25; Mattill, 1920).

The handling of intravenous glucose has been observed to be abnormal (Chaudhuri, 1948; Holmes & Trowell, 1948; Gomez et al, 1955; Bose et al, 1946;
Niemeyer and Meneghello, 1950; Slone et al, 1961; Baig and Edozien, 1965; Hadden, 1967, Oxman, 1968) but Bowie (1964) was the first to draw attention to the normal tolerance in marasmus. Gillman et al (1961), using $^{14}$C glucose and $^{14}$C pyruvate, showed that labelled glucose, whether derived from pyruvate or injected as such, persists longer in the blood of kwashiorkor than in control children. In healthy fasting subjects the blood sugar is maintained at normal levels for 12 to 24 hours (Thompson & King, 1957). In the absence of gluconeogenesis, however normal blood sugar levels could be maintained for only about six hours (Bell et al, 1959).
In their earlier studies, Waterlow and Weisz (1956), reported some rather inconsistent results; by chemical estimation and histological examination they thought the liver glycogen was increased in protein calorie undernutrition in children; later on, however, their group (Alleyne and Schullard, 1969) found liver glycogen to be decreased in these children. Some other authors also reported increased liver glycogen (Stuart et al, 1958; Fletcher, 1966; Salazar de Souza, 1959). Holmes and Trowell (1968) indicated impaired glycogen synthesis. Alleyne and Schullard (1969) found that the amount of liver glycogen was significantly reduced in malnourished children and increased after recovery. The glycogen content of muscle was low in malnutrition and was correlated with the concentration of potassium (Alleyne et al, 1969a). With recovery there was a marked overshoot to levels higher than normal, and in the fully recovered child the values were found to be normal (Alleyne and Schullard, 1969; Nicol et al, 1969 b).

Reduced glucose-6-phosphatase activity was observed in malnourished children (Mukherjee and Nath, 1957; Salazar de Souza, 1959; Fletcher, 1966). But Alleyne et al (1969) reported a high level of glucose-6-phosphatase activity in malnourished children, the level decreased with recovery. Phosphoglycogenase activity of the liver was also reduced (Salazar de Souza 1959). Liver phosphorylase activity showed no change in malnourished children. (Alleyne and Schullard, 1969).
PLASMA INSULIN LEVEL IN MALNUTRITION

Ehrlich and Bambers (1964) found the fasting plasma insulin levels of 6 normal children to be similar to adult levels. Slone, Soeldner, Steinks and Crigler (1966) reported low fasting serum insulin levels in 13 normal children between the ages of 3 and 9 years. Grant (1967) found that fasting serum insulin concentration of 36 children (3 months to 14 years) rose progressively with increasing age.

The development of immunoassay techniques has made it possible to study plasma insulin response to various stimuli. Baig and Edozien (1965) showed that fasting plasma insulin levels were low in kwashiorkor and rose with recovery, but in their study there was a normal insulin response to intravenous glucose. Hadden in Uganda (1967) on the contrary reported that plasma insulin levels were low in marasmus; but normal in kwashiorkor. In Jamaica James and Coore (1970) and Milner (1971) have shown that plasma insulin is low initially and that the rise in response to intravenous glucose is absent or after clinical recovery the response, although significantly improved, is still much lower than in normal children. Milner (1971) could not demonstrate an increase in plasma insulin after intravenous injection of glucagon. Rao and Raghuramulu (1972) reported normal insulin levels in children suffering from kwashiorkor. Following an oral glucose load, there was virtually no increase of insulin, although the blood sugar increased to almost twice the fasting level.
In marasmus in children, the adrenal glands were small; the decrease in weight has been as much as 60% although the loss in total body weight was, perhaps about 30% (Lucien, 1908). The glands were darker than normal, had a firm consistency and the surface were granular in appearance. On histological examination the capsule appeared thickened, the trabeculae increased and the cortex was sclerotic; the glands appeared to be hypoactive. The cortical cells, especially in the zona reticularis were often atrophied and devoid of fat. The capillaries in the zona reticularis were dilated. Marfan (1921) also reported small adrenal glands in infantile athrepsia. Nicolaeff (1923) found small adrenal glands in autopsies of starved Russian children.

Bablet and Canet (1952) reported that the adrenal glands were enlarged and fragile in children suffering from protein-calorie undernutrition, on the other hand Trowell et al (1954), reported that they were atrophic and devoid of lipid. Gillman and Gillman (1951) presented some evidence that initially there was hyperfunction, and only terminally exhaustion and atrophy. Chatterjee and Sengupta (1960) reported that the glands were necrotic with patchy loss of lipid and Campbell (1956) noted that the glands were unaffected. Contrary results were reported
for the excretion of 17-hydroxycorticosteroids in urine in such children. Castellanos and Arroyave (1961) reported great reduction in the excretion of 17-hydroxy-
corticosteroids in children suffering from kwashiorkor. But Lurie and Jackson (1962) found only slightly reduced excretion and concluded that evidences of significantly reduced adrenal function are rare in infantile malnutri-
tion.

Malnourished children had consistently high levels of plasma cortisol which fell with recovery (Alleyne & Young, 1966, 1967). There was a significant negative correlation between blood glucose and plasma cortisol values. Similar findings have also been reported from India (Rao, et al, 1968). Cortisol levels were significantly higher in marasmic children than in those with kwashiorkor; in both groups the levels fell after treatment.

Plasma 17-OH corticosteroids have been measured in malnourished Egyptian children and also found to be elevated (Abassy et al, 1967). Najjar et al demonstrated no adrenal insufficiency or decreased functional reserve by using ACTH stimulation test.

There is decreased binding of cortisol in the plasma of malnourished infants (Leonard & MacWilliam, 1964).