Dr C. Gopalan has spearheaded the campaign against undernutrition in India for nearly four decades. His contributions towards the cause of betterment of the nutritional status of the poor have benefited India and other developing countries and have inspired movements for the eradication of undernutrition among them.

Nearly 40 years ago, after a brilliant academic career at the Madras Medical College leading to a Doctoral Degree in Medicine, Dr Gopalan was poised for a lucrative practice as a clinician. Around that time India was rocked by the worst famine in its history—the Bengal famine—in which several thousand people died of starvation. The impact of the famine moved Dr Gopalan to combat undernutrition among the poor.

He founded the National Institute of Nutrition in India in 1960 and was its Director till 1974. The institute is now recognized to be one of the best of its kind in the world and has made major contributions towards understanding nutritional problems affecting the poor.

As Director-General of the Indian Council of Medical Research (1974–79), he provided a new orientation to medical research in the country and encouraged investigation into problems on communicable diseases and those related to poverty and undernutrition.

Dr Gopalan initiated the series of Asian Congresses of Nutrition in 1970. He was primarily responsible for the formation of the Federation of Asian Nutrition Societies. He has also been President of the International Union of Nutritional Sciences and was the first Chairman of the Regional Advisory Committee on Medical Research for South East Asia (WHO, SEARO).

Dr Gopalan’s research contributions include over 200 papers and over a dozen books on nutrition. He is a Fellow of the Royal Society. At present he is the Director-General of the Nutrition Foundation of India.

Kwashiorkor and Marasmus: Evolution and Distinguishing Features

C. Gopalan

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Nearly 14 years ago, an international group of scientists met in Jamaica to discuss what was then termed the problem of “Protein Malnutrition”. In these intervening years a great deal has been written on the subject, but is evident that considerable controversy and confusion still surround many aspects of this problem.

An important step in our better appreciation of the problem in recent years is the recognition that in all considerations of protein adequacy the question of calorie intake is of the utmost importance. Professor Platt has forcefully reminded us of the old dictum that proteins and calories are closely interdependent. He has deplored the tendency to equate the term kwashiorkor with protein malnutrition, and has advocated the concept of protein–calorie deficiency, which will include in its ambit such different clinical syndromes as marasmus and kwashiorkor and marasmic kwashiorkor.

Protein–calorie deficiency leads to two distinct clinical syndromes—kwashiorkor and marasmus. In recent years there have been some extremely elegant experimental studies which have convincingly shown how variations in the caloric intake modify and condition the effects of protein deficiency. It has been now clearly demonstrated that syndromes analogous to marasmus and kwashiorkor can be produced in experimental animals by appropriate dietary manipulations.

On the basis of experimental studies it has now been postulated that a deficiency of protein with adequate or more than adequate calories leads to kwashiorkor, while deficiency of calories leads to marasmus. The protein–calorie ratio in the diet is held to be of crucial significance in this regard. Some workers speak of a spectrum of protein–calorie malnutrition, one end of which is represented by marasmus, and the other by kwashiorkor.

The application of experimental results to human situations is often a difficult exercise and has to be attempted with considerable caution and circumspection. The observations which I intend to present pertain to poor Indian communities among whom both marasmus and kwashiorkor are frequently encountered. These observations will show that the current hypotheses which seek to explain the differential pathogenesis of marasmus and kwashiorkor, purely on the basis of differences in the protein–calorie ratio in the diets in these two states, do not meet all the facets of the situation.

### TABLE I  KWASHIORKOR AND MARASMUS: SALIENT FEATURES

<table>
<thead>
<tr>
<th>Feature</th>
<th>Marasmus</th>
<th>Kwashiorkor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of maximal incidence</td>
<td>6–18 months</td>
<td>12–48 months</td>
</tr>
<tr>
<td>Emaciation</td>
<td>++ +</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Oedema</td>
<td>Absent</td>
<td>+ to + +</td>
</tr>
<tr>
<td>Fatty infiltration of liver</td>
<td>0 to ±</td>
<td>+ +</td>
</tr>
<tr>
<td>Skin changes</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Almost normal</td>
<td>Markedly lowered</td>
</tr>
<tr>
<td>Serum enzymes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>Normal</td>
<td>Markedly lowered</td>
</tr>
<tr>
<td>Amylase</td>
<td>Normal</td>
<td>Lowered</td>
</tr>
<tr>
<td>Esterase</td>
<td>Slightly lowered</td>
<td>Lowered</td>
</tr>
<tr>
<td>Serum lipids:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Normal</td>
<td>Lowered</td>
</tr>
<tr>
<td>Non-esterified fatty acids</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Response to epinephrine</td>
<td>Exaggerated</td>
<td>Lowered</td>
</tr>
<tr>
<td>Serum urea</td>
<td>Normal</td>
<td>Lowered</td>
</tr>
<tr>
<td>Copper in serum</td>
<td>Normal</td>
<td>Lowered</td>
</tr>
<tr>
<td>Hair copper</td>
<td>Normal</td>
<td>Lowered</td>
</tr>
<tr>
<td>Urinary urea/total urine nitrogen</td>
<td>Above 65%</td>
<td>Below 50%</td>
</tr>
<tr>
<td>Increase in body weight after high protein</td>
<td>Poor</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>and calorie intake during the first 4 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
generally lower than that of kwashiorkor, though, apparently, this is not the case in Jamaica. The reduction in serum protein and serum albumin levels is of a somewhat lower order in marasmus than in kwashiorkor. Serum lipase, amylase and esterase concentrations are better preserved in marasmus than in kwashiorkor. Liver biopsies reveal that the liver is more or less normal in marasmus, in contrast to kwashiorkor where marked fatty change is a characteristic feature. Total 24-hour urinary nitrogen, as well as the ratio of urea nitrogen to total nitrogen, are significantly higher in marasmus than in kwashiorkor. Blood urea and blood cholesterol are significantly reduced in kwashiorkor as compared to marasmus. Non-esterified free fatty acid levels are, apparently, elevated in both conditions. Ferritin is present in serum in kwashiorkor, but not in marasmus. My colleague, Dr. S. G. Srikantia, will discuss this observation in greater detail at a later stage in this colloquium. The fasting blood sugar levels are apparently normal in both conditions, but the response to epinephrine is poor in kwashiorkor but not in marasmus.

A comparison of the non-essential amino acid ratios in marasmus and kwashiorkor, using the one-dimension chromatography technique of Whitehead and Dean (1964), failed to reveal any consistent difference between the two conditions. The ratio was either normal, raised or lowered in kwashiorkor, and in some cases of kwashiorkor the ratios actually increased after treatment (Fig. 1). In marasmus the values did not appear to be raised. So we do not subscribe to the claim that this test is of diagnostic value. The alanine-glutamine ratio was low in kwashiorkor and increased after treatment. The picture was exactly opposite in the case of marasmus.

The total 24-hour hydroxyproline excretion in urine was reduced in cases of kwashiorkor. However, the value, when expressed in terms of creatinine, was not significantly different from that obtained in normal children. We are, therefore, of the view that this reflects only changes in body weight and does not indicate a specific change in collagen metabolism.

Most of the differences between kwashiorkor and marasmus which I have listed above can be directly related to the central fact that in marasmus the functional integrity of the liver is relatively better preserved than in kwashiorkor.

It will thus be clear that marasmus and kwashiorkor, in their classical forms, are two clearly distinguishable syndromes. The important question is whether they represent two distinct and different diseases with different aetiological backgrounds and calling for different methods of approach with regard to prevention and control, or whether they represent two distinct facets of the same disease. Our observations bearing on the question of evolution and natural history of these two syndromes, as they occur in our region, may throw light on this question.

EVOLUTION

Conclusions as to the evolution of kwashiorkor or marasmus have generally been based on histories obtained from cases of kwashiorkor, or on animal experiments. It is obvious that reliable information on the evolution of these states will be possible only through field studies of communities among whom kwashiorkor and marasmus are common.

Many of you here are aware of the extensive survey of the incidence of protein-calorie deficiency which we carried out some years ago in four South Indian States (Someshwar Rao et al., 1959). That survey revealed that among the poorest sections of the populations, 1–2 per cent of children of preschool ages suffered from frank signs of kwashiorkor at any given time. The incidence of frank marasmus in the same community was twice as high. That survey, however, did not provide direct information as to the evolution of these syndromes.

We have recently undertaken an intensive study of a poor rural community. Nearly 2,000 children below 5 years of age have been examined. In a representative sub-sample of this group, careful diet surveys were carried out by trained investigators. The salient results of these studies have been set out in Table II.

A comparison of the weights of these children at different ages with corresponding data for American children shows the extent of growth retardation in this group. The daily protein intake varied from 1.9 g/kg in infancy to around 1.5 g/kg in the fourth and fifth years. The protein was almost solely derived from cereals (rice and/or millet) in the later age group, while in the earlier age group breast milk contributed a significant proportion. In terms of “reference protein”, therefore, the pro-

![Fig. 1. Non-essential/essential amino acid ratio in five children during treatment for kwashiorkor](image-url)
### Table II: Protein and Calorie Intakes of Poor South Indian Children

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number surveyed</th>
<th>Mean weight (kg.)</th>
<th>Reported normal American weight (kg.)</th>
<th>Protein intake g./24 hr.</th>
<th>Calorie intake kcal./24 hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–12 months</td>
<td>126</td>
<td>6.7</td>
<td>9.6</td>
<td>12.6</td>
<td>593</td>
</tr>
<tr>
<td>1–2 years</td>
<td>418</td>
<td>7.8</td>
<td>11.4</td>
<td>13.5</td>
<td>645</td>
</tr>
<tr>
<td>2–3 years</td>
<td>328</td>
<td>9.1</td>
<td>13.6</td>
<td>19.9</td>
<td>868</td>
</tr>
<tr>
<td>3–4 years</td>
<td>394</td>
<td>10.7</td>
<td>15.7</td>
<td>19.4</td>
<td>904</td>
</tr>
<tr>
<td>4–5 years</td>
<td>578</td>
<td>12.4</td>
<td>17.4</td>
<td>18.9</td>
<td>858</td>
</tr>
</tbody>
</table>

Protein intake in the latter age group was about 1.0 g./kg. These figures would appear just adequate in terms of actual body weights, but are clearly lower than the latest recommendations of the W.H.O./F.A.O. Expert Group (1965), when expressed in terms of "ideal body weight".

The daily caloric intake ranged from around 90 kcal./kg. body weight in the earlier age group to around 80 kcal./kg. in the later age group. These intakes are clearly less than the figure of 100–110 kcal./kg., which is generally considered adequate. Thus, even on the basis of the actual body size of the children, the caloric intake must be considered inadequate. In the light of these figures for caloric intake the protein inadequacy of the diets must, in fact, be considered to be greater than the protein intake figures alone would indicate.

The calories obtained from protein accounted for 8 per cent of total calories—a percentage that could be expected of dietaries which are almost solely based on rice, wheat or millets.

Two salient features which emerge from the foregoing observations are: firstly, there is a remarkable attempt to restrict body growth to a level which will be in keeping with the availability of protein and calories. Growth retardation in these children is an attempt at adaptation to the protein-calorie deficiencies; secondly, and this is more important from the practical standpoint, the main bottleneck in the current dietary situation is calorie inadequacy. An increase of about 30 per cent in the intake of even cereal-based diets would not only correct the calorie inadequacy but also promote a better utilization of dietary protein, without distorting the present protein–calorie ratio. The prevailing picture of protein–calorie malnutrition in these communities would thereby be considerably mitigated. It is essential to emphasize this point in these days of unceasing quest for protein concentrates and protein isolates.

Twenty-three frank cases of kwashiorkor were seen among the group of 1,800 children below 5 years, giving a prevalence of 1.3 per cent. This is similar to the prevalence rate of kwashiorkor observed in our more extensive earlier survey. The number of cases of marasmus in this group depends on the criteria employed. Practically all children in the community showed growth retardation associated with varying degrees of emaciation. Two to three per cent of children showed particularly severe degrees of emaciation and could be designated as cases of marasmus. The body weights of the children with kwashiorkor (after disappearance of oedema), and with marasmus, were nearly 60 per cent of the average weights for the corresponding age groups in the community.

The important point I wish to emphasize here is that the most careful investigations failed to show that the dietary pattern of the children who developed kwashiorkor or marasmus was qualitatively different from those of other children in the community. They had all subsisted on the same type of cereal-based diets as the rest of the children in the community. The quantities consumed were at the lower limits of the range of intakes obtaining in the community. In particular, we are in a position to state categorically that there was no evidence whatsoever that the children who developed kwashiorkor had been "force-fed" or that their mothers had tended to "push" starchy foods. On the contrary, we found that some of these children, for some weeks prior to the onset of frank kwashiorkor, had subsisted on even smaller quantities of the same cereal-based diets that they had previously taken. Thus, if there was any change at all in the diet, it was in the direction of further restriction of calories and proteins without any change in the protein–calorie ratio.

As far as this community was concerned, therefore, the development of the two forms of protein–calorie malnutrition could not be explained on the basis of the hypothesis: predominant calorie deficiency—marasmus; predominant protein deficiency with adequate or more than adequate calories—kwashiorkor.

We have also made a longitudinal study of nearly 300 children from birth for periods extending up to 3 years. Ninety of these children have now been followed up for over 3 years. These children also belonged to the same poor socio-economic group. They are visited at fortnightly intervals in the first year and at monthly intervals thereafter. The object of this study was to elucidate the natural
history of protein–calorie malnutrition in the community and to assess the possible contributory role of dietary factors and infections in this process. Out of the 90 children followed up for 3 years, seven developed frank signs of kwashiorkor during the study.

The dietary patterns of these children conformed to the picture presented earlier; the diet in all cases could be considered protein–calorie deficient. The growth was apparently satisfactory up to about the fourth month; thereafter, the growth curve levelled off and varying degrees of emaciation were found in all the children. In some, the emaciation was so marked as to justify the designation “marasmus”. Some children showed “moon face” and dyschromotrichia, a picture which would correspond to what some workers call “pre-kwashiorkor”—a rather misleading name, since these children on follow-up did not necessarily develop kwashiorkor. Some children developed frank signs of kwashiorkor (Figs. 2 and 3). The growth pattern and the dietary pattern of the children who developed kwashiorkor and of those who did not, were not materially different. There was no evidence that children who developed kwashiorkor had been either force-fed or having a diet any different from that of other children in the community. Five of the seven children who developed kwashiorkor had recurrent bouts of diarrhoea and dysentery for some days, resulting in loss of appetite and further restriction of their diets. These children were fed their usual diets but in smaller quantities. In one case an attack of chicken-pox preceded the development of kwashiorkor. In another, the development of kwashiorkor was gradual and could not be attributed to any special factors.

These longitudinal studies again confirmed that there was no striking qualitative differences in the dietary pattern or in the protein–calorie ratio of diets between cases of marasmus and kwashiorkor on the one hand and the undernourished children in the community on the other. It would seem that cases of marasmus and kwashiorkor were the end results of more severe degrees of the same type of protein–calorie deficiency prevalent in the rest of the community.

In extensive nutrition surveys among communities of poor children subsisting on almost uniform protein–calorie-deficient diets, kwashiorkor, marasmus and “nutritional dwarfism” are often found to coexist. It is our experience that in such a malnourished community, roughly 1–1.5 per cent of children below 5 years show evidence of kwashiorkor, about 2–3 per cent are frankly marasmic and the rest show varying degrees of growth retardation and emaciation. Further, marasmic children may develop kwashiorkor (marasmic kwashiorkor) and children with kwashiorkor may present the picture of marasmus after shedding their oedema. Marasmus and kwashiorkor thus coexist in the same community. Marasmus and kwashiorkor can also be seen in the same child while continuing on the same diet, at different points of time.

It will thus be clear that marasmus and kwashiorkor, as they are seen in our area, are not the same as experimental marasmus and kwashiorkor, induced by caloric deficiency or force-feeding respectively. I am aware, however, that human counterparts of experimental “marasmus” induced in animals through feeding low-calorie diets, and of experimental “kwashiorkor” induced through force-feeding protein-deficient diets, exist in other situations. Marasmus has been frequently seen in children fed on small quantities of milk. It is also probable that Jamaican kwashiorkor, which has been reported to be associated with a high caloric intake, and whose peak age incidence has been claimed to be similar to marasmus (Garrow, 1966), may be looked upon as the human counterpart of “experimental kwashiorkor” brought about by force-feeding. I consider, however, that the great majority of cases of kwashiorkor in India, probably in Indonesia and possibly in the Middle East, cannot be explained on this basis. We have necessarily to enlarge our concept of the pathogenesis of kwashiorkor.

**PATHOGENESIS OF KWASHIORKOR: A HYPOTHESIS**

It may be expected that when a child is subjected to the stress of protein–calorie deficiency
its tissues respond to the stress in a manner that would enable it to "adapt" itself to the deficiency. In fact, growth retardation and restriction of physical activity are obvious clinical manifestations of such adaptation. The preservation of functional and structural integrity of the liver may be considered as yet another instance of adaptation. The biochemical mechanisms at the cellular level which are involved in such adaptation and the precise role of hormonal and other factors therein, still require to be carefully elucidated. Waterlow (1959) has shown in experiments with labelled amino acids that in animals on a low-protein diet, liver protein becomes more highly labelled than in animals on a normal diet. In a further extension of this work, Waterlow and Stephen (1966) showed that the rat adapts itself to a low protein diet by an alteration in the pattern of protein synthesis. They demonstrated that protein turnover was "maintained at more or less normal levels in those organs which may be considered most essential for life at the expense of those such as muscles and skin, which are less essential". Other biochemical evidence of such adaptation to low-protein diets have also been provided by Mariani, Spadoni and Tomassi (1963), who found an increase in the activity of amino acid activating enzymes in the liver of animals on protein-deficient diets.

Children in a poor community subsisting on protein-calorie-deficient diets may be expected to represent various stages of such adaptation, depending on the degree and duration of protein-calorie deprivation. "Nutritional dwarfism" may be considered to represent the relatively milder effects of such adaptation, while marasmus may be considered to reflect the extreme effects of that process, the farthest limit is what Garrow (1959) picturesquely called the "contraction of the metabolic frontiers".

As was pointed out earlier, the hormonal factors involved in such adaptation are as yet unclear. Waterlow and Stephen (1966) have suggested a possible role of insulin. Platt, Heard and Stewart (1964) have adduced evidence of decreased insulin activity in young pigs on a protein-calorie-deficient diet. The results of studies on cortisol levels in kwashiorkor are apparently conflicting. Pimstone and co-workers (1966) have reported raised growth hormone levels in kwashiorkor. On the other hand, Monckeberg and co-workers (1963) obtained good response in cases of marasmus after injection of growth hormone and suggested that in this syndrome there is an endocrine-controlled adaptation to the shortage of food. The metabolic adjustments geared to protect the liver-in marasmus at the expense of muscle are shown by the observation that it is extremely difficult to get a marasmic child under treatment to put on weight.

It may be postulated that there may sometimes be a failure of adaptation. Kwashiorkor may be considered such a failure of adaptation. The biochemical mechanisms which are usually invoked to protect the essential tissues like the liver, pancreas and intestines at the expense of less essential muscle, have failed; functional and structural damage to the liver follows, and the signs and symptoms of kwashiorkor which are largely attributable to this become evident. What are the factors that bring about such dysadaptation? One may postulate that force-feeding or the administration of excess calories in the face of protein deficiency may be one such factor. This will explain "experimental kwashiorkor" induced by force-feeding and the Jamaican kwashiorkor associated with excessive calories and unaccompanied by emaciation. On the other hand, dysadaptation may also be brought about by a sudden further exaggeration or by continued prolongation of the stress of protein-calorie deficiency. This sequence will explain the pathogenesis of cases of kwashiorkor as seen in our country. Most of the cases of kwashiorkor here are likely to be cases of marasmic kwashiorkor associated with a considerable degree of muscle wasting and emaciation.

It may be expected that in a poor community exposed to the stress of protein-calorie deficiency the great majority of the children will need to develop a mild degree of adaptation (nutritional dwarfism), but a considerable number will show the extreme results of adaptation (marasmus) and a small number will show the effects of dysadaptation (kwashiorkor). This is generally the picture which is seen in poor Indian communities.

Though this hypothesis would appear to be largely based upon circumstantial evidence, I would like to mention some experimental results that lend support to it. It has been shown by Ramalingaswami, Deo and Sood (1961) that "experimental kwashiorkor can be induced in monkeys in a matter of a few weeks by force-feeding them a protein-deficient diet". On the other hand, we had shown earlier (Srikantia and Gopalan, 1959) that kwashiorkor can be induced in monkeys without force-feeding, provided the animals are maintained for prolonged periods of time on protein-calorie deficient diets. The details of this study will be presented later in this colloquium by Dr Srikantia.

We have shown that marasmic children have levels of plasma cortisol significantly higher than those in children suffering from kwashiorkor (unpublished data), and we have also observed that the administration of cortisol to monkeys force-fed low protein diets postpones considerably the development of fatty livers. More clinical and experimental studies are obviously necessary before the validity of this "adaptation" hypothesis
is established. We have some studies under way to examine these aspects of the problem.

REFERENCES


This paper, published nearly a quarter of a century ago and still widely quoted, had a very important influence on all of us working on childhood malnutrition. After 1935, when Williams described the development of kwashiorkor in a west African child displaced from the breast by a new baby and put to feed on starchy paps, most of us believed that the underlying cause of the syndrome was protein deficiency. In the minds of many this belief was elevated to the status of a dogma, according to which protein was the most important limiting factor in the diets of Third World children. Consequently, an enormous amount of time and money was devoted to the development of protein-rich supplements for young children. To the world at large the scientific validity of this policy appeared to be guaranteed by the support that it received from the Protein Advisory Group of the United Nations.

Gopalan’s paper showed very clearly that the theoretical basis of this activity was untenable, although he was careful to caution against generalizing to the world as a whole from his results in India. His was the first community study involving a population of children large enough to produce a number of cases of kwashiorkor and marasmus. Up to that time almost all the work on these conditions had been hospital-based and little attention had been given to their evolution and natural history. Measurements of food intake showed that the cereal-based diet of these village children was marginally deficient in both energy and protein by the standards current at that time. Moreover—and this is the key point—there was no difference, quantitatively or qualitatively, in the diets of the children who developed kwashiorkor on the one hand and marasmus on the other.

The hypothesis that kwashiorkor represents a breakdown of adaptation does not take us very much further because, in my opinion, a marasmic child can hardly be regarded as adapted. However, that is a question of terminology; the important point of principle that emerged from Gopalan’s study was that the different clinical pictures are to a large extent determined by differences in the host response rather than in the nutritional environment. Such an interpretation is consistent with the well recognized variability in the energy and protein requirements of individual children, although the basis of this variability is still unknown.

This paper of Gopalan’s, therefore, had an impact in three ways: it showed the artificiality of regarding malnutrition, as it evolves in a community, as a single-factor disease; it restored the balance when the pendulum had swung too far towards exaggerating the importance of protein; and it displayed the dangers of basing public health policy on inadequate scientific evidence.

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