Fig. 2—Histopathology of the spinal cord of monkey C on day 18 post-infection.
Neuronophagia and gliosis in the anterior horn of the cervical cord. (Hæmatoxylin and eosin; reduced to 2/3 of \(\times250\).)

Fig. 3—Histopathology of the spinal cord of monkey E on day 35 post-infection.
Disappearance of neurons and severe hyperplasia of small vessels with cuffings. (Hæmatoxylin and eosin; reduced to 2/3 of \(\times100\).)

Discussion

Our findings suggest that A.H.C. virus isolated in Japan is neurovirulent in monkeys to a degree comparable to that of live attenuated poliovirus vaccine.

REFERENCES

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SERUM-ALBUMIN CONCENTRATION AND THE ONSET OF KWASHIORKOR

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Summary

Various major biochemical changes, closely related to the pathological abnormalities found later in severe kwashiorkor, all start to develop at about the same time. These include low insulin, high cortisol and growth hormone, low \(\alpha_2\) and \(\beta\) globulin, low \(\beta\)-lipoprotein, and very low valine and alanine concentrations in the serum, as well as a reduced serum-colloidal-osmotic-pressure and associated early clinical signs such as a "moonface". In the type of protein malnutrition found in Uganda this critical phase begins after
serum-albumin concentration has fallen below 3·0 g. per 100 ml.

**Introduction**

Contrary to our expectations and the general conclusion of most other nutritionists, a study in Uganda has reopened the possibility that the measurement of serum-albumin concentration might be important in the detection and assessment of early malnutrition. Although we confirmed that decreasing serum-albumin concentrations did not correlate well with general tissue-wasting, we were able to demonstrate that they reflected the susceptibility of a child to oedema. Early signs of oedema, including a "moon-face", were detected with increasing frequency after the albumin concentration had fallen below 3·0 g. per 100 ml. On this evidence alone, however, it would not have been justifiable to come to any final decision about the value of serum-albumin measurements for nutritional surveys; additional, more objective information was required.

One of us has proposed that before a measurement can be claimed as a true assessment of subclinical malnutrition it must first be shown to have significance or potential significance in terms of essential body function. In other words, a state of malnutrition must be characterised in terms of malfunction; malnutrition is not just a synonym for dietary deprivation.

It has been recognised for many years that at the kwashiorkor end of the protein-energy malnutrition spectrum, malfunction centres around widespread biochemical abnormalities, including distorted serum-protein and aminoacid fractionation patterns and also an altered hormonal balance, as demonstrated by high fasting concentrations of cortisol and growth hormone but low insulin values. These biochemical changes eventually result in pathological abnormalities. For example, low albumin concentrations lead to reduced plasma-colloidal-osmotic-pressures which are closely associated with the development of oedema. Equally important are the low serum-β-lipoprotein concentrations which are believed to be the primary cause of the fatty liver, another major feature of kwashiorkor.

In Uganda a three-year prospective study into the pathogenesis of kwashiorkor has just been completed. One of the purposes of this investigation was to establish the developmental time-course of these biochemical and pathological abnormalities. It was reasoned that a child must surely be judged to be subclinically malnourished when dietary deprivation has continued for so long that the overall metabolic pattern characteristic of clinical kwashiorkor has begun to appear. We envisaged that this information would enable us to say which of the simple biochemical measurements was capable of giving an accurate indication of the onset of this critical phase and, as a consequence, to suggest functionally relevant guidelines for the interpretation of the measurement.

We describe the value and clinical significance of serum-albumin measurements as an indication of the onset of the critical phase of kwashiorkor.

**Patients and Methods**

The children studied were either patients with severe kwashiorkor admitted to the metabolic ward or outpatients attending a child-welfare clinic at Namulonge, 20 km. north of Kampala. The total number investigated was 326, but not every measurement was made on each child. Many of the outpatients were part of the prospective longitudinal survey described previously.

Blood-samples were collected after an overnight fast in the ward and during the morning at the clinic, but, since traditionally little or no breakfast is eaten, these samples too were virtually from fasting children.

Serum-albumin was measured by an automated colorimetric technique and β-lipoprotein was measured immunologically; valine and alanine were estimated by...
an automated column-chromatographic system. Hormonal assays were carried out as follows: cortisol, by the protein-binding radioassay method; insulin and growth hormone, using radioimmunoassay methods. More complete details of the hormone assays are given elsewhere. Colloidal osmotic pressure was determined using an electronic membrane micro-osmometer manufactured by H. Knauer, West Berlin, Germany.

Results

By studying children from both the ward and the outpatient clinic we were able to obtain serum samples covering the whole range of nutritional states from normal to severe kwashiorkor. In the figure, the results of seven of the serum measurements plus the data previously obtained for the frequency of the moonface sign have been ranked according to the corresponding albumin concentration. Except for the aminoacids and insulin, there was no major change while serum-albumin concentration was falling to 3 g. per 100 ml., but, rather surprisingly, as soon as albumin concentration dropped below this value all the measurements became affected simultaneously and showed a distinct deviation towards the pattern found in severe kwashiorkor.

The initial reductions in serum-valine concentrations to around 150 µmole per litre and the large increases in alanine concentrations once children are weaned on to low-protein/high-carbohydrate diets are well-established phenomena, but the concentration of both aminoacids reached a plateau at a new level and, as with the other components, there was no deviation from this value until albumin concentration fell below 3 g. per 100 ml. Similarly, with insulin there was an initial rise in fasting levels, probably in response to the high carbohydrate content of the traditional diet, but not until albumin concentration fell below 3 g. per 100 ml. did insulin concentrations start to fall to the low values typical of severe kwashiorkor.

Discussion

The simultaneous onset of so many metabolic abnormalities illustrates the widespread and complex nature of the processes which are involved in the onset of clinical kwashiorkor in a child. It is not the purpose of the present report to discuss the interrelationships between these processes but to point out the value of serum-albumin measurements as a marker for this critical switch in metabolic balance.

Our preliminary investigation indicated that 3 g. per 100 ml. was the critical serum-albumin concentration as far as the appearance of early oedematous signs was concerned. This conclusion was confirmed by the coincidence of the pattern of change for colloidal osmotic pressure with that for the appearance of the moonface sign. The reason why colloidal osmotic pressure did not start to fall sooner was that initially the oncotic consequences of the gradual fall in albumin concentrations was cancelled out by concomitant increases in the concentrations of the serum-globulins (mainly γ-globulins). Below an albumin concentration of 3·0 g. per 100 ml., however, no further rise in globulin concentration occurred, in fact, because of reductions in ζ and β globulins, total globulin concentration exhibited a significant fall in concentration, contributing to the reduction in colloidal osmotic pressure.

The drop in serum-β-lipoprotein concentration as soon as serum-albumin concentration had fallen below 3·0 g. per 100 ml. indicates that at the same time as the child is becoming gradually more susceptible to oedema, he is also becoming susceptible to the development of a fatty liver. The onset of these serum-protein changes might well be related to the alterations in the pattern of the serum-aminoacids, which in turn are probably initiated by the changes in hormonal balance; this possibility is discussed elsewhere.

Although there is now good evidence that the functionally significant "cut-off" point for serum-albumin concentration as a marker for the onset of the final pathology is 3·0 g. per 100 ml., many paediatricians and nutritionists would probably wish for a measurement which could pick out a child at an earlier stage. To some extent serum-albumin can do this as well. The Interdepartmental Committee on Nutrition for National Defense, whilst recommending that only values below 2·8 g. per 100 ml. should be judged as actually deficient, said that normal concentrations should be above 3·5 g. per 100 ml., and for this reason they termed values between 2·8 and 3·5 g. per 100 ml. as low. Certainly, serum-albumin concentrations can begin to fall into this range quite early during malnutrition, even while growth might still be taking place at a normal rate.

There are, of course, measurements which are much more sensitive than serum-albumin to dietary deprivation and its immediate consequences. Such measurements tend to be of two types, those which are a direct response to the amount of protein in the diet—for example, urinary urea excretion and the urea/creatinine ratio—and those which indicate a metabolic adaptation to a changed dietary environment in the way that the initial changes in serum valine and alanine concentration or a slightly raised aminoacid ratio are the consequence of eating diets with a low-protein but high-carbohydrate content. As long as the meaning of such measurements is understood they serve a useful role, but in practice their very sensitivity can make interpretation difficult. Even quite abnormal values can become normal again after a short period on a good diet.

In our opinion it would be an advantage if, when future biochemical tests for the assessment of nutritional status are proposed, it were made clear whether they are essentially measurements of dietary adequacy or whether they can actually detect a malnourished child. If the latter is claimed, we hope that it is on the basis of the malnutrition/malfunction principle and that the measurement has been justified in terms of the overall pathology. The type of system described in the present report for assessing the significance of albumin should be adaptable to most other measurements.

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Hepatic damage and death from overdose of paracetamol

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Summary

Of a series of sixty patients admitted after paracetamol overdose, forty-nine developed liver damage. Seventeen patients progressed to hepatic encephalopathy, and twelve of these died from fulminant hepatic failure. All but two of the patients with bilirubin levels above 4 mg per 100 ml by the 3rd–5th day developed encephalopathy. It is suggested that the degree and prognosis of the liver damage in the first few days can be assessed from the serum-bilirubin and prothrombin-time. Histology of liver-biopsy specimens of those who recovered showed severe centrilobular necrosis and collapse, but no patient had progressed to cirrhosis. Although most patients appeared well in the first 3 days after ingestion, it is likely that the liver damage can be prevented only in the first 24 hours.

Introduction

Paracetamol (acetaminophen, N-acetyl-p-aminophenol) was first isolated over 100 years ago, but was not included in the British Pharmacopoeia until 1960. The first British cases of hepatotoxicity from overdose taken with suicidal intent were not published until 1966. Studies in rats at that time showed that in large doses paracetamol was a predictable hepatotoxin, and since then fatal hepatic necrosis in man after an overdose has been reported from several countries. There have been sixteen non-fatal cases and one fatal case described from Scotland—and indeed the incidence of paracetamol overdose in Britain is increasing rapidly.

During 16 months (March, 1971, to June, 1972, inclusive), fifty-seven patients were admitted to the Liver Unit, King's College Hospital, after an alleged overdose of paracetamol; in forty-six there was evidence of hepatic necrosis. Nine patients died from fulminant hepatic failure, and this was the cause of death in three other patients seen between 1967 and 1970. We describe here the clinical findings in these sixty patients, with particular reference to the assessment of the likely prognosis during the first few days after ingestion of the drug. This is important when considering the use of possible techniques for removing the drug from the body, including hemodialysis.

Clinical Findings

There were forty-five females and fifteen males, aged 15–58; thirty-nine patients were aged less than 30, and eleven were teenagers. A third were admitted on the 1st or 2nd day after ingestion of the overdose, but most were referred later when signs of severe liver damage developed on the 3rd–6th days. Nineteen patients had allegedly taken alcohol or another drug (barbiturate, nitrazepam, diazepam, or chloridiazepoxide) at the same time as the paracetamol, but the severity of their liver damage was no different from that of those who had ingested paracetamol alone. The doses of paracetamol claimed to have been ingested ranged between 13 and 100 g, but this did not correlate with the degree of hepatic damage (table).

Within a few hours of ingestion of the drug most of the patients experienced anorexia, nausea, and vomiting, and this persisted in varying severity for the 1st and 2nd days. There was no clouding of consciousness at first unless one of the sedative drugs had also been taken. Indeed, most patients felt quite well on the 2nd and 3rd days, and this persisted in varying severity for the 1st and 2nd days. There was biochemical evidence of liver damage in all except eleven patients, but the severity of the damage varied considerably. In seven patients only the serum-aspartate-aminotransferase (S.G.O.T.) was abnormal (range 53–365 i.u. per litre), while only one had an abnormal prothrombin-time ratio, and in another the only abnormality was a raised serum-bilirubin. In the remaining forty patients all biochemical tests became abnormal, and in seventeen there was, in addition, clinical evidence of severe liver damage, with progression on the 3rd to 5th days to fulminant hepatic failure as defined by Trey et al., with the signs of hepatic encephalopathy (namely, hepatic flap and fetor, and mental confusion). Day coma ensued in fifteen of these, and twelve died—one on the 4th day after ingestion of the overdose, ten on the 6th–11th days, and one on the 18th day.

The clinical features in these patients differed in no way from those seen in patients with fulminant hepatic failure due to other causes. Severe bleeding from the gastro-