

## THE TREATMENT AND PREVENTION OF KWASHIORKOR

### CLINICAL TRIAL OF A NEW HIGH-PROTEIN FOOD SUPPLEMENT

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Kwashiorkor can be prevented by a diet that contains enough protein of animal origin. The best sources of such protein are milk, cheese, meat, eggs and fish,<sup>1</sup> but these foods may be too costly or not readily available in the countries where kwashiorkor occurs. Despite more intensive and efficient methods of farming, it is doubtful whether the supply of these products will ever suffice to satisfy the demands of an expanding world population and a higher standard of living. For these reasons attempts have been and are being made in various parts of the world to produce high-protein foods from vegetable or mixed animal and vegetable sources.<sup>1-3</sup>

The qualities required by any new food given to prevent protein malnutrition have been enumerated by Dean.<sup>4</sup> The food: (a) should be acceptable to the children and their parents; (b) should be cheap and, where possible, processed from local ingredients; (c) should keep well even in poor conditions of storage and mix easily with the staple foods; (d) should have the appearance of a food designed for small children, but not for the adult members of the family; (e) should be bland, and capable of being used at times as a fluid drink; (f) should be rich in proteins, minerals and calories; (g) should contain protein of high quality which yields a complete mixture of all the amino acids needed for the synthesis of new body protein by a growing child.

Such a product, 'pronutro', has been produced in Durban. It is composed mainly of skimmed milk, soya bean, peanut meal, fish flour, and whole maize flour, together with bone calcium, iodized salt, iron salt, and food yeast. The food has a protein content of 21.5% and a caloric value of 365 calories per 100 G. In addition it contains vitamins A, B<sub>1</sub>, B<sub>2</sub>, and niacin. Pronutro is precooked and has a bland flavour. It keeps well, can readily be made into a thick gruel or porridge by the addition of water, and can be added to other staple foods. The raw materials are grown or processed in South Africa. Older members of the family are less likely to consume this food at the expense of the child than is the case with skimmed-milk powder.

The calculated aminogram of the food, expressed as grams per 100 grams food, is: arginine 1.5 G., histidine 0.55 G., cystine 0.31 G., isoleucine 1.23 G., leucine 2.06 G., lysine 1.33 G., methionine 0.41 G., phenylalanine 1.12 G., threonine 0.92 G., tryptophan 0.27 G., valine 1.31 G., and tyrosine 1.02 G.

The basic qualities of the food are obvious. This investigation was planned in order to compare the response, over a period of 28 days, of 2 groups of children suffering from kwashiorkor, the one on pronutro and the control group on skimmed-milk powder. The quantities of these foods were calculated so that each child obtained 2 G.

protein per lb. body weight per day. After 7 days, sufficient mealie meal porridge was added to the diets of each group to raise the caloric intake to 50 calories per lb. body weight per day. No other foods were allowed.

#### MATERIAL AND METHODS

During the 7-month period between 1 April and 31 October 1960, 149 African children suffering from kwashiorkor were admitted to one ward. All these showed<sup>5</sup> (1) a dietary history suggesting protein malnutrition, (2) oedema associated with hypo-albuminaemia not explained by renal, cardiac or other disease, (3) retarded growth, (4) peevish mental apathy, and (5) variable dermatoses. Thirteen had had kwashiorkor previously. No case was rejected unless the child weighed more than 30 lb., exceeded 3 years of age, or had active pulmonary tuberculosis. Children who were moribund on admission or had complications such as dysentery, pneumonia or anaemia were not excluded.

#### Sociological Background

(a) *Separation of the child from its mother.* Forty-nine of 135 children had been separated from their mothers during the preceding 6 months, for 1 month or more.

TABLE I. DETAILS ABOUT SEPARATION OF MOTHER AND CHILD

| Duration of separation in months |   |   |   |   |    | Person in charge of child |      |       | Cause of separation of mother and child |                           |                   |                  |           |             |
|----------------------------------|---|---|---|---|----|---------------------------|------|-------|---|---------------------------|-------------------|------------------|-----------|-------------|
| 1                                | 2 | 3 | 4 | 5 | 6  | Grandmother               | Aunt | Other | Works during day                        | Works in another district | Illness of mother | Illness of child | Abandoned | Mother dead |
| 6                                | 7 | 6 | 4 | 2 | 17 | 21                        | 11   | 10    | 16                                      | 15                        | 2                 | 3                | 5         | 1           |

Details of these separations were recorded in 42 cases and are given in Table I.

(b) *Legitimacy.* Sixty-two of 109 children were known to be illegitimate, but 27 of them were being supported by the father. In many instances he was living with the mother.

#### Dietary History

All, except 8 children, had been breast fed. Although the proportion of those wholly breast fed declined from about 80% at 3 months of age to 40% at 6 months and 20% at 9 months, almost half were still partially breast fed at 1 year of age.

After weaning, maize was the basis of the diet and was usually prepared as a porridge. In some cases it was the

only food, but in others cow's milk, dried milk powder or *maas* was given in inadequate amounts or erratically. A few children had small portions of meat or fish, but never more often than once a week and sometimes only once a month.

#### Growth Failure

The children were weighed after the oedema had disappeared and the weights were compared with a 'normal'

TABLE II. DISTRIBUTION OF CASES ACCORDING TO PERCENTAGE OF EXPECTED WEIGHT (146 CHILDREN)

|   |  | Percentage |    |    |    |    |    |    |
|---|--|------------|----|----|----|----|----|----|
|   |  | 100        | 90 | 80 | 70 | 60 | 50 | 40 |
| 1 |  | 8          | 23 | 46 | 37 | 24 | 7  |    |

curve constructed from the figures of Phillips<sup>6</sup> and Salber.<sup>7</sup> As shown in Table II the vast majority were underweight.

#### Infections and Complications

Many children were found to have complications on admission to the ward; others developed them during their stay in hospital (Table III). The most troublesome

TABLE III. INCIDENCE OF INFECTIONS AND COMPLICATIONS IN 111 CURED CASES

| Group        | Measles | Bronchopneumonia | Otitis media | Gastro-enteritis | Clinical dysentery | Amoebic dysentery | Megaloblastic anaemia | Transitory erythroblastopenia | Iron-deficiency anaemia | Normocytic normochromic anaemia | Ascariasis | Trichuriasis | Giardiasis |
|--------------|---------|------------------|--------------|------------------|--------------------|-------------------|-----------------------|-------------------------------|-------------------------|---------------------------------|------------|--------------|------------|
| Skimmed milk | 18      | 5                | 4            | 6                | 25                 | —                 | 7                     | 4                             | 4                       | 7                               | 17         | 2            | 8          |
| Pronutro     | 14      | 8                | 8            | 1                | 3                  | 1                 | 6                     | 1                             | 5                       | 9                               | 13         | 4            | 5          |
| Total        | 32      | 13               | 12           | 7                | 28                 | 1                 | 13                    | 5                             | 9                       | 16                              | 30         | 6            | 13         |

was measles, which became endemic in the ward despite the routine administration of gamma globulin to non-immunes.

#### Medical Procedures

Every child was examined and assessed, usually by the same individual, soon after admission to the wards, and the history and physical examination were recorded on special forms. The cases were classified as mild, moderate or severe. The chief difference between severe and moderate cases was the presence of marked apathy. The original assessment was not often revised, but, as Dean<sup>8</sup> recorded, there was a tendency on admission to underestimate severity. If an alteration of the grading was necessary, this was made within the first 2 or 3 days. The distribution of the cases between the 2 trial groups is shown in Table IV.

TABLE IV. DISTRIBUTION OF CASES ACCORDING TO SEVERITY

| Group        | Severe | Moderate | Mild | Total |
|--------------|--------|----------|------|-------|
| Pronutro     | 15     | 42       | 13   | 70    |
| Skimmed milk | 13     | 51       | 15   | 79    |

$\chi^2 = 0.618$  with 2 degrees of freedom (d.f.). Not significant.

After the clinical examination and assessment, the cases were allocated by random sampling to the pronutro or skimmed-milk group (70 to the pronutro group and 79 to the skimmed-milk group).

The children were weighed naked at the same time each day and all were given: (1) tetracycline syrup, 5 ml. 6-hourly for the first week; (2) multivitamin syrup (NPA pharmacopoeia), 5 ml. *b.d.* throughout their stay in the ward; and (3) gamma globulin (0.1 ml. per lb. body

weight) except when there was a definite past history of measles.

The routine investigations included examination of the urine and stools, Mantoux and Volmer patch tests and an X-ray film of the chest.

#### Laboratory Investigations

On the day of admission, or more commonly on the next day, the following estimations were performed: (1) blood count; (2) serum proteins, bilirubin and cholesterol; (3) blood sugar; and (4) electrolytes — sodium, potassium and chlorides.

Thereafter a blood count and estimations of the serum proteins, cholesterol and blood sugar were repeated at weekly intervals.

#### Preparation of Feeds

The volume of water added to the pronutro and the skimmed-milk powder was such that 1 oz. of either feed provided 1 G. of protein.

1. *Pronutro*. 6½ oz. of pronutro were mixed with 36 oz. of water to make a feed of 40 fl. oz. The food was prepared every 12 hours. This feed has a caloric value of 680 and a protein content of 40 G.

2. *Skimmed-milk formula*. 4 oz. of skimmed-milk powder and 2½ oz. of sugar were mixed with 36 fl. oz. of water to make a feed of 40 fl. oz. This feed has a caloric value of 690 and a protein content of 40 G.

3. *Mealie meal porridge*. 3 oz. of mealie meal were mixed with 20 oz. of water and boiled for 10 minutes. This formed a thin porridge of 20 fl. oz. when warm, but set when allowed to cool. The caloric value was 300.

Special weights for the amounts of pronutro, skimmed-milk powder, sugar, and mealie meal were provided to reduce the possibility of error.

The daily ration for each child consisted of: (a) 2 oz. per lb. body weight of pronutro or skimmed milk, (b) 1 oz. per lb. body weight of porridge.

#### Definition of Terms

The following terms are derived from those described by Brock, Hansen *et al.*,<sup>5</sup> but are not identical with them.

(a) *Initiation of cure*. This is the stage when the skin lesions have begun to heal, the serum albumin has risen above 2.5 G. per 100 ml., there is no oedema, and the general condition has vastly improved.

(b) *Partial initiation of cure*. The general condition of these patients has improved by the 28th day, they are now interested in their surroundings, but a trace of oedema and/or hypo-albuminaemia persists. If treatment is continued cure will probably be fully initiated within 1-2 weeks.

(c) *Failures*. These children have made little or no progress after 28 days and may even have deteriorated. They are oedematous, their serum albumin is less than 2.5 G. per 100 ml., and the skin lesions may show no signs of healing.

(d) *Gain in weight*. The difference between the weight on the 28th day, and the lowest weight after clinical oedema had disappeared.

## RESULTS

### 1. Clinical

On the 28th day of treatment all children were examined and a clinical assessment was made to determine whether

TABLE V. RESULTS OF TREATMENT

|                 | I  | PI | F | D  | Total |
|-----------------|----|----|---|----|-------|
| Pronutro .. ..  | 44 | 9  | 4 | 13 | 70    |
| Skimmed milk .. | 54 | 2  | 2 | 21 | 79    |

I=cure initiated, PI=cure partially initiated, F=treatment failed, D=patient died.  
 $\chi^2=7.50$  with 3 d.f. Not significant. (5% significance value is  $\chi^2=7.81$ .)

treatment had initiated cure, partially initiated cure, or failed. The results are shown in Table V.

Expressed as percentages, on the 28th day cure had been initiated in 63% of the children treated with pronutro and 68% of those treated with the skimmed-milk formula. This difference is not statistically significant.

## 2. Time Needed to Initiate Cure

In many cases cure had been initiated before the 28th day of treatment. Table VI shows that cure was initiated

TABLE VI. TIME WHEN CURE WAS INITIATED

| Group           | 2nd week |    | 3rd week |    | 4th week |    | 5th week |     | 6th, 7th and 8th weeks |     |
|-----------------|----------|----|----------|----|----------|----|----------|-----|------------------------|-----|
|                 | No.      | %  | No.      | %  | No.      | %  | No.      | %   | No.                    | %   |
| Pronutro .. ..  | 7        | 13 | 21       | 40 | 16       | 30 | 5        | 9   | 4                      | 8   |
| Skimmed milk .. | 9        | 15 | 30       | 51 | 16       | 27 | 2        | 3.5 | 2                      | 3.5 |

slightly sooner in the skimmed-milk group.

## 3. Weight Gain

The average daily gain in weight after disappearance of oedema was  $1\frac{1}{2}$  oz. in the skimmed-milk group compared with  $1\frac{1}{2}$  oz. in the pronutro group.

## 4. Duration of Oedema

Oedema persisted for a longer time in the pronutro group. On the average, it dispersed after  $13\frac{1}{2}$  days compared with  $9\frac{1}{2}$  days for the controls.

## 5. Duration of Stay in Hospital

After the 28th day all the children who had been cured or partially cured were transferred to a convalescent hospital. There they were given the ordinary hospital diet without restrictions or additions. They were examined at regular intervals by an experienced member of the staff who did not know the previous dietary history, and discharged when she thought they had recovered. The average duration of the stay in hospital of the pronutro and skimmed-milk groups was 44 and 43 days respectively.

## 6. Serum Cholesterol

The diets used in this trial had a low fat content. Matthew and Dean<sup>8</sup> have stated that a diet rich in protein, but containing no fat, will cause the rapid removal of cholesterol abnormally retained in the liver, but will not be favourable to the synthesis of new cholesterol. They described 3 patterns of cholesterol values in kwashiorkor. A 'peak' pattern was shown by about half of the patients under treatment, most of the remainder showed a gradual rise, and a few a very small rise or none at all. Similar patterns were obtained in this series, except that two-thirds of the patients in both groups showed the peak pattern. The mean values of the serum cholesterol are shown in Table VII.

## 7. Serum Proteins

The steady upward trends of the concentrations of serum albumin and total serum proteins in both groups are shown in Tables VIII and IX. Skimmed milk produced a more rapid increase of serum albumin and total serum-protein concentrations than pronutro. These increases

TABLE VII. MEAN VALUES OF SERUM CHOLESTEROL IN MG. PER 100 ML.

| Group              | Day of treatment |     |     |     |
|--------------------|------------------|-----|-----|-----|
|                    | 1                | 8   | 15  | 22  |
| Skimmed milk .. .. | 82               | 118 | 114 | 100 |
| Pronutro .. ..     | 78               | 96  | 89  | 86  |

TABLE VIII. MEAN VALUES OF SERUM ALBUMIN IN G. PER 100 ML.

| Group              | Day |     |       |       |       |
|--------------------|-----|-----|-------|-------|-------|
|                    | 1-2 | 8-9 | 15-16 | 22-23 | 28-29 |
| Skimmed milk .. .. | 1.6 | 2.3 | 2.6   | 2.9   | 3.1   |
| Pronutro .. ..     | 1.6 | 1.8 | 2.2   | 2.5   | 2.7   |

Significant at 1% level.

became evident by the end of the first week, and the higher averages for skimmed milk were maintained throughout the period of the trial. These differences are statistically significant at the 1% level.

TABLE IX. MEAN VALUES OF TOTAL SERUM PROTEIN IN G. PER 100 ML.

| Group              | Day |     |       |       |       |
|--------------------|-----|-----|-------|-------|-------|
|                    | 1-2 | 8-9 | 15-16 | 22-23 | 28-29 |
| Skimmed milk .. .. | 4.2 | 5.7 | 6.2   | 6.5   | 6.8   |
| Pronutro .. ..     | 4.3 | 4.9 | 5.4   | 6.0   | 6.0   |

Significant at 1% level.

There was no significant difference in the haemoglobin and blood-sugar levels in the 2 groups.

## 8. Mortality Rates

During this investigation 3 children who were convalescent died from measles. These deaths have been excluded. This correction reduces the total number of deaths to 35. Details of these deaths are shown in Table X.

TABLE X. TIME AND NUMBER OF DEATHS

| Group          | Within 48 hours | Between 3rd and 28th day | After 28 days | Total | Death rate |
|----------------|-----------------|--------------------------|---------------|-------|------------|
|                |                 |                          |               |       |            |
| Pronutro .. .. | 3               | 10                       | 2             | 15    | 21%        |

$\chi^2=3.018$  (2 d.f.). Not significant.

If the deaths that occurred within 48 hours of admission are also excluded, the death rates are reduced to 20% in the skimmed-milk group and 18% in the pronutro group. This difference is not significant ( $\chi^2$  almost zero). Even if the 'failures' are added to the deaths, the difference is still not statistically significant ( $\chi^2=5.84$ ).

## 9. Postmortem Findings

Autopsies were performed in 35 cases. The complications found are shown in Table XI.

Histological examination of the liver showed diffuse fatty changes in all cases.

## DISCUSSION

This investigation has been based on the assumption that if a food cures kwashiorkor it will also prevent the disease. Because the amounts required for cure are so much greater than for prevention, we feared that ill and feeble children would be unable or unwilling to eat their ration of pronutro. In practice there was no such difficulty, and by the second or third day most children took the strange new food eagerly.

The nurses soon noticed a difference between the stools of the 2 groups. Those fed the skimmed-milk mixture had loose, yellow and fairly frequent stools, in contrast to the semi-solid, brown and less numerous stools of pronutro. A common and frustrating experience at our outpatient clinic is that the mothers of malnourished children so



TABLE XI. COMPLICATIONS FOUND AT AUTOPSY (35 CASES)

| Group        | Bronchopneumonia | Otitis media | Pleurisy | Empyema | Acute colitis | Amoebic dysentery | Non-specific ulceration of ileum | Pyelonephritis | Hydropic degeneration of tubules | Sinus thrombosis | Thrombocytopenia | Thrush | Ascariasis |
|--------------|------------------|--------------|----------|---------|---------------|-------------------|----------------------------------|----------------|----------------------------------|------------------|------------------|--------|------------|
| Skimmed milk | 12               | —            | —        | —       | —             | —                 | —                                | —              | —                                | —                | —                | —      | —          |
| Pronutro     | 10               | 1            | —        | —       | —             | —                 | 1                                | 1              | —                                | —                | —                | —      | —          |
| Total        | 22               | 1            | 1        | 1       | 1             | 1                 | 2                                | 3              | 1                                | 1                | 1                | 1      | 1          |

often refuse to continue powdered skimmed-milk feeds because they cause diarrhoea. These same mothers might be reassured by the more solid stool produced by pronutro.

While the trial was in progress, delegations from the various kwashiorkor relief committees in local African housing schemes or nearby Reserves were invited to visit the wards. The purpose of the experiment was explained to them and they were able to see for themselves how the children fared. Great stress was laid on the point that this was a cheap, but not an inferior, product. Furthermore, they were told that the food would only become available to the public when its value had been proved. During a ward round they saw how easily pronutro porridge was made by the addition of water, and that no cooking was needed. They appreciated that this would be a useful economy in the urban areas where paraffin is used for fuel. The visitors helped to feed some of the patients. All agreed that the porridge was palatable. They found nothing about the food or its preparation that conflicted with local customs. In our experience pronutro has been acceptable to the children, the nurses, and groups of representative Africans.

A recent survey of kwashiorkor in Durban<sup>9</sup> showed that the mortality rate at King Edward VIII Hospital had fallen from 53.6% in 1955 to 35.8% by 1959. In the present investigation the overall mortality rate was 23.5%. The most probable reason for this improvement is that the ward was never allowed to become overcrowded and closer medical and nursing care was possible. It may be argued that milder forms of kwashiorkor were admitted during the winter months, but the above survey showed that the mortality rate remained surprisingly constant throughout the year.

A high incidence of associated infections is a feature of kwashiorkor as it occurs in Durban. These conditions aggravate the disease and delay recovery, but it would be unrealistic to exclude such complicated cases when evaluating any treatment. Thompson,<sup>10</sup> who conducted a similar trial in Uganda, expressed the same views.

It is shown that measles, bronchopneumonia and 'clinical dysentery' were the common complications of kwashiorkor. Although there were approximately the same number of cases of measles and bronchopneumonia in the 2 groups, there was a marked disparity in the incidence of 'clinical dysentery'. This diagnosis was made whenever pus and mucus were seen on microscopic examination of the stools and no pathogens were found. It occurred in 25 of the 79 children in the skimmed-milk group, but only 3 times in the 70 patients given pronutro. A possible

explanation is that these children did not in fact have dysentery, but were suffering from sugar intolerance,<sup>2</sup> although the presence of pus cells in the stools was thought to be more suggestive of dysentery.

At the end of 28 days of treatment no significant difference between the efficacy of pronutro and the skimmed-milk formula was demonstrated when the number of cures, deaths and the average daily weight gains were compared (Tables V and X). The duration of stay in hospital was the same. However, there was a significant difference between the regeneration of total serum proteins and serum albumin in the 2 groups (Tables VIII and IX).

The clinical effects of the slower regeneration of serum albumin were shown in 2 ways, namely, persistence of oedema for a longer time and some delay in the initiation of cure in the pronutro group. This slower regeneration of serum proteins should not, in our opinion, prejudice the usefulness of pronutro. Similar results were reported by Scrimshaw and Bressani<sup>1</sup> in Guatemala, where they treated patients with 'acute kwashiorkor' with INCAP vegetable mixtures 8 and 9. The latter is now being sold commercially and is regarded as a significant contribution to the problem of preventing protein malnutrition in that area. Likewise, pronutro should prove a valuable and cheap protein supplement in South Africa. In order to avoid any suggestion that milk is an unsuitable food, pronutro should perhaps be prescribed as a substitute for porridge rather than as a replacement for milk.

#### SUMMARY

1. The qualities of pronutro, an inexpensive, locally produced, high-protein food derived from mixed animal and vegetable sources, are described.
2. A controlled clinical trial in the treatment of 149 children with kwashiorkor shows that pronutro matches skimmed milk in the percentage of cures, death rate and duration of hospital stay, but that the regeneration of serum proteins is slightly delayed.
3. Pronutro should prove to be a valuable protein supplement for the prevention of kwashiorkor in South Africa.

We are indebted to Prof. H. L. Wallace for help in the preparation of this paper; to Dr. F. Walt for advice about the day-to-day management of the patients; to Prof. J. Wainwright and his staff for the pathological and biochemical investigations; and to Mr. S. E. Cruise of the Department of Mathematics, University of Natal, for assistance in the statistical analyses. A clinical trial depends on the cooperation of the nursing staff, and we wish to acknowledge the support given by Sister May Yingwana and Staff Nurse Vesta Maku.

We are indebted to Messrs. Hind Bros., Durban, for unlimited supplies of pronutro for the purpose of this trial.

Finally, we thank Dr. S. Disler, Medical Superintendent, King Edward VIII Hospital, for facilities.

#### REFERENCES

1. Scrimshaw, N. S. and Bressani, R. (1961): *Fed. Proc.*, **20**, suppl. 7, 80.
2. Dean, R. F. A. (1952): *Brit. Med. J.*, **2**, 791.
3. *Idem* (1960): *J. Pediat.*, **56**, 675.
4. *Idem* (1960): *E. Afr. Med. J.*, **37**, 378.
5. Brock, J. F., Hansen, J. D. L., Howe, E. E., Pretorius, P. J., Davel, J. G. A. and Hendrickse, R. G. (1955): *Lancet*, **2**, 355.
6. Phillips, H. T. (1953): *Arch. Dis. Childh.*, **28**, 226.
7. Salber, E. J. (1957): *Hum. Biol.*, **29**, 12.
8. Matthew, C. E. and Dean, R. F. A. (1960): *J. Trop. Pediat.*, **4**, 135.
9. Scragg, J. and Rubidge, C. (1960): *Brit. Med. J.*, **2**, 1759.
10. Thompson, M. D. (1955): *Ibid.*, **2**, 1366.