PROTEIN REQUIREMENTS OF INFANTS*

2. MARASMUS

BY

W. F. YOUNG, M.D., D.C.H., E. A. BISHOP, M.B., B.S., D.C.H., EVELYN M. HICKMAN, M.Sc., Ph.D., and YVONNE J. WILLIAMS, M.D.

(From the Children's Hospital and Department of Paediatrics and Child Health, University of Birmingham)

Failure to gain or actual loss of weight is a common condition in young infants which has been a subject of discussion for centuries, and in the past there was a tendency to regard wasting as a clinical entity. This conception is entirely wrong (Parsons, 1924); it is but a symptom of some underlying condition and is in this respect comparable with other common symptoms such as vomiting, convulsions, and diarrhoea, none of which is regarded as a disease *sui generis*. The causes of severe wasting may be classified under two main headings, (a) insufficient food, and (b) presence of infection. Insufficient food may be due to quantitative or qualitative defects in the diet or it may be the result of impaired absorption from the alimentary tract due to disease or diarrhoea. It may also be due to insufficient food reaching the intestine, as in abnormal conditions of the oesophagus or of the stomach, for example, pyloric stenosis. It is difficult in some cases to separate lack of food from the presence of infection as the cause of wasting, because vomiting and diarrhoea and intolerance of food may be the result of infection and so introduce the starvation factor. Conversely, the infant who is not receiving adequate food is more liable to infection than the one whose nutrition is normal. In treating states of malnutrition it is always necessary to discover the underlying cause, for unless this is removed, the measures designed to arrest the progress of wasting will probably fail.

Recent studies have shown that gross protein depletion may occur in wasted subjects. Starvation deprives the body of the protein which is normally retained by growing infants, and it may be assumed that infection and injury accelerate protein metabolism in infants as has been described in adult man and in animals (Cuthbertson, 1944; Himsworth, 1946), causing the well recognized association

between infection and marasmic states. The losses due to accelerated protein metabolism may be severe, and it is thus easy to understand why an infant may 'fall away' during the course of a week or two. Furthermore, mobilization of tissue protein seems to be accelerated when the body-weight falls below 80 per cent. of its expected level in infants, and there is a rise in the basal metabolic rate (Talbot, 1921; Fleming, 1921). Fleming has suggested that in the first stages of atrophy the loss of weight is taking place mainly at the expense of metabolically inactive tissue (fat) but that as it advances there is a greater wastage of metabolically active tissue (muscle). A still later stage of wasting in infants (below 70 per cent. of their expected weight) is associated with a fall in the basal metabolic rate. The functions of the respiratory and of the cardiovascular systems may then begin to fail with slowing of the pulse and respiration rate and a subnormal temperature. The patient's condition is critical and a return to normal function is seldom achieved. There is, therefore, a very small margin of safety in treating infants who have wasted to 80 per cent. of their expected weight, and every effort must be made to improve their condition or at least to prevent its deterioration. Tolerance for food is low, and the dilemma may arise of choosing between the risks of a period of semi-starvation while the diet is being built up slowly, and those of over-feeding with the consequent development of diarrhoea and vomiting. The accepted practice is to begin with a low intake of total calories supplying only the maintenance requirements of about 25-35 calories/lb./day (50-70/kg./day) and to be guided by the progress of the patient in increasing them to his full requirements for gaining weight. The fluid intake is maintained at $2\frac{1}{2}$ -3 oz./lb./day (150-180 ml./kg./day) and the calorie intake is increased by strengthening the feeds. The intake of fat is usually low (concentrations below 2 per cent.) unless human milk is being given, because experience has shown that fat is badly tolerated, but carbohydrate is allowed in high concentrations (7-12 per cent.). The protein intake varies. It is often recommended that the amount of protein

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contained in undiluted cows' milk should be given, but that tolerance to this amount of curd should be acquired by strengthening the milk and water mixtures gradually. In the past this feeding method has given good results in a majority of cases at the Children's Hospital, Birmingham. A number of infants, however, have continued to lose weight and have died before their nutrition had begun to improve; often pneumonia was the terminal event. The prognosis for such patients has changed since sulphonamide drugs and penicillin have been available. Nevertheless, anxiety about the nutrition of babies admitted to hospital with very severe degrees of wasting has continued, lest they should succumb to infection or to a failure of metabolism before improvement in their nutrition has been achieved.

When preparations of protein digests became available it was appreciated that they might be used to provide an easily assimilable food and to augment the protein intake of marasmic infants at the beginning of their treatment. Young infants suffering from malnutrition or infection may have hypochlorhydria (Marriott and Davidson, 1923; Parsons, 1924), and relative pancreatic insufficiency (Andersen, 1942). It is, therefore, rational to give them hydrolysed protein which can be absorbed by the alimentary tract without much digestive activity. Furthermore, the mixture of polypeptides and amino-acids of which the digests are composed is freely soluble and no curd is formed in the stomach. Information concerning the phase of recovery from malnutrition in infancy is scanty, and the maximum rate at which repair can be achieved has not been studied in relation to dietary intake. The protein intake should be high enough to allow for nitrogen retention to proceed at a greater rate than it does during periods of normal growth and, in planning the feeds to be used in this

investigation, it has been considered that 4-6 g. protein/kg./day would probably be adequate in this respect. Preparations of casein hydrolysate for oral administration became available in 1944 and a preliminary trial of three of these was arranged forthwith. Amounts to increase the concentration of protein by 1 per cent. or 2 per cent. were added to the cows' milk mixture or to the expressed breast milk which was being used to feed twenty-five infants. Most of the infants took the feeds well without disturbance of alimentary function. Some had four to five bowel movements a day and the stools were somewhat relaxed, but the patients continued to thrive and to gain weight satisfactorily without any change in the composition of the feeds. Since hydrolysed casein was found to be well tolerated by infants, it was planned to use it systematically for feeding marasmic babies. One of the preparations used in the trial, 'casydrol',* was used throughout the subsequent investigations.

Feeds for Marasmic Infants

The composition of the cows' milk feeds which have been used is shown in table 1. They have been arranged in stages so that the diet can be changed gradually from a milk mixture containing part of the protein as hydrolysed casein to one consisting of undiluted cows' milk. The composition with regard to fat and carbohydrate has also been graded. If expressed human milk was being used 1 per cent. or 2 per cent. of hydrolysed casein was added to increase the total concentration of protein to 2½-3½ per cent. The cows' milk feeds were acidified in order to augment the acid in the stomach of infants likely to have hypochlorhydria.

* 'Casydrol' is prepared by Genatosan Ltd., but it should be noted that the manufacturers have changed the composition of 'casydrol' so that it is no longer 100 per cent. hydrolysed casein.

TABLE 1
COMPOSITION OF FEEDS USED FOR MARASMIC INFANTS

	Milk Formulae		(%)			Calories and Protein (g.) supplied (2½-3 oz./lb./day)	
			Protein	Carbo- hydrate	Fat	Calories/kg. bodyweight	Total Protein/kg. bodyweight (g.)
Stage I Calories/oz.=17	Lactic acid milk	4 oz.	3·7	8·4	1·3	92-110	5·6-6·7
	Water	8 oz.					
	'Dextri-Maltose'	6 dr.					
	Casein hydrolysate	9·6 g.					
Stage II Calories/oz.=20	Lactic acid milk	6 oz.	4·2	9·1	2·0	107-129	6·3-7·6
	Water	6 oz.					
	'Dextri-Maltose'	6 dr.					
	Casein hydrolysate	9·6 g.					
Stage III Calories/oz.=20	Half-cream 'Lacidac'	12 dr.	3·7	8·7	2·0	106-127	5·6-6·7
	Water	12 oz.					
	Sugar	3 dr.					

Thrush and other organisms are often present in the pharynx, oesophagus and stomach, and *Esch. coli* is sometimes prevalent in the stomach and upper bowel of infants who are suffering from hypochlorhydria. The growth of all these organisms may be inhibited by an acid medium. The stronger feed, Stage II, was introduced as soon as toleration of the weaker mixture had been established in order to give the higher caloric intake of 20 cal./oz. (see table 1). The substitution of the Stage III feed, in which whole protein entirely replaces hydrolysed casein, was delayed until a considerable amount of progress had been made, judged by a regular gain in weight, but it was always made before the patients were discharged from hospital. This last change in the feed was made gradually over a period of several days, and if the stools became bulky the transition was delayed.

Vitamin supplements were given as follows:

'Tab. benerva co.' 1 daily	aneurin (B1)	1 mg.
	riboflavine	1 mg.
	nicotinic acid amide	15 mg.
	Vitamin A	4,000-7,000 units.
Ascorbic acid 50 mg. daily	Vitamin D	700-1,200 units.
'Adexolin' m. 6-10 daily		

Iron supplements were given to four infants, two of whom were premature, but they were not used as a rule.

If infection had been present or if the patient did not begin to gain weight, fresh blood or plasma transfusions were sometimes given during the first week or two of treatment.

Subjects for the Investigation

Observations were made on seventy-nine young infants between two and seventeen weeks of age who weighed 80 per cent. or less of their expected

weight at the beginning of treatment. Twenty-one of these were excluded from the final analysis of results for reasons which will be given later. The clinical material for the main investigation therefore consisted of fifty-eight infants, and these were divided broadly into infants suffering from pyloric stenosis (insufficient food), and infants suffering from marasmus due to other causes (chiefly infection). Each of these divisions contained some infants who made steady progress and others whose progress was retarded by complications, such as infection. The infants were therefore finally divided into the following four groups.

Group No.	Condition	Progress	No. of cases
1	Pyloric stenosis on admission	Uncomplicated	20
2	" " " "	Complicated	15
3	Marasmus due to other causes	Uncomplicated	6
4	" " " "	Complicated	17

Four of the infants (two in Group 2 and two in Group 4) in our investigation weighed between $4\frac{1}{2}$ and 5 lb. at birth and must be regarded as having been born prematurely. Consequently, their progress should not be compared with that of infants born at term, and the observations made on these babies have been recorded (P) on the figures in order to distinguish them. There were a number of other infants who weighed between 5 and 6 lb. at birth, but the observations made on them have been assessed together with those of babies with

TABLE 2
METHOD OF GRADING STRENGTH OF FEEDS AFTER OPERATION FOR PYLORIC STENOSIS

Period after operation (hours)	Composition of feed		Feeding intervals	Volume of feed per 24 hours
	Milk formula (Stage II in Table 1)	5% 'Dextri-Maltose' (= NaCl)		
0-12	4 drams	4 drams	Two-hourly · 12	$12\frac{3}{4}$ oz.
12-24	5 drams	4 drams		
24-36	6 drams	4 drams		
36-48	8 drams	4 drams	Two-hourly · 12	$16\frac{1}{2}$ oz.
48-60	10 drams	4 drams		
60-72	12 drams	4 drams		
4th day	2 oz.	—	Two-hourly · 10	20 oz.
5th day	$2\frac{1}{2}$ oz.	—	Three-hourly · 8	20 oz.
6th day	3 oz.	—	Three-hourly · 7	21 oz.

higher birthweights, since the development of malnutrition in our patients was judged to have been little affected by variations in their size at birth.

Pyloric stenosis was treated surgically, and the course of infants (Groups 1 and 2) during the post-operative period is described. A special feeding schedule (see table 2) was arranged for them by which a quick transition was made to Stage II feeds (see table 1). By following this schedule the patients received the undiluted milk mixture (Stage II) on the fourth post-operative day. More caution was exercised in feeding a few of the very ill babies, but all cases were being given the undiluted feed by the end of the fifth day after operation. The volume of the feeds was adjusted to supply 150 ml./kg. body-weight (2½ oz./lb. body-weight) daily by the end of the first week. Salt was added to the feeds to supply about 1.0 g. NaCl daily until the silver nitrate test for chlorides in the urine gave a flocculent deposit. The infants whose marasmus was due to causes other than pyloric stenosis (Groups 3 and 4) were treated according to their special needs, and many of them were given sulphadiazine and penicillin to combat infection.

The other twenty-one marasmic infants who received casein hydrolysate were excluded from the main analysis of the results for the following reasons. Six infants had casein hydrolysate added to human milk instead of to the lactic acid milk mixtures which were used for the majority of the infants; good results were obtained. In eleven cases the feeding schedule was not followed systematically, but only once was casein hydrolysate discontinued because it was suspected to be the cause of vomiting. The remaining four omissions were infants found at necropsy to have been suffering from a congenital abnormality, namely, hydrocephalus, stenosis of the lower end of the oesophagus, and cystic fibrosis of the pancreas (two cases), which had caused persistent failure to thrive.

Intake of Food

The average intake of food for the cases in Groups 1 and 3 during the early weeks of treatment is shown in table 3, but the intakes of patients in Groups 2 and 4 have not been averaged because they were more variable. Although the intake was often reduced for a short period in a patient suffering from infection, it was soon increased so that most of the infants in Groups 2 and 4 were receiving similar amounts to those in Groups 1 and 3 for the greater part of their course. Table 3 shows that during the second week after operation the average daily intake for patients in Group 1 reached 122 calories and 6.8 g. protein/kg./day and that during subsequent weeks the same intake was maintained. The average intake of the patients in Group 3 was somewhat greater than this after the third week. The casein hydrolysate feeds were replaced earlier by stronger milk mixtures (Stage III) for the patients in Groups 1 and 3 (two to three weeks) than for those in Groups 2 and 4 (three to twelve weeks) whose progress was retarded by complications.

Assessment of Wasting and Progress in Response to Treatment

The degree of wasting and progress towards recovery were assessed by comparing the patient's weight with that of healthy infants of the same age. Statistical studies of weight throughout infancy have not been made in Great Britain, but data for the white races in the U.S.A. are available from the results of a study which was made in Iowa (Jackson and Kelly, 1945). The average weight for male and female infants at the 50th percentile and one standard deviation below and above it (the 16th and 84th percentiles respectively) on the Iowa weight curves have been taken as the standard range for infants of different ages in the present investigation.

TABLE 3
AVERAGE DAILY CALORIE AND PROTEIN INTAKE OF INFANTS IN GROUPS 1 AND 3 DURING FIRST SIX WEEKS OF TREATMENT

Weeks	First week		Second week		Third week		Fourth week		Fifth week		Sixth week	
Groups	1	3	1	3	1	3	1	3	1	3	1	3
No. of Cases	20	6	20	6	19	6	15	5	9	4	8	3
Calorie intake/ kg. bodyweight/day	84	100	122	124	121	126	122	136	125	134	123	134
Total Calorie intake/day	257	287	400	384	424	412	452	475	472	486	512	497
Protein intake/ kg. bodyweight/day	3.88 g.	4.90 g.	6.84 g.	7.40 g.	6.12 g.	7.40 g.	6.06 g.	7.72 g.	6.08 g.	7.40 g.	6.08 g.	6.84 g.
Total Protein intake/day	12.6 g.	14.4 g.	22.6 g.	22.6 g.	21.5 g.	24.4 g.	22.5 g.	28.0 g.	23.2 g.	26.8 g.	25.3 g.	24.6 g.

Fig. 2.—Weight curves of fifteen marasmic infants, admitted with pyloric stenosis, compared with Iowa standard weight curves of normal infants.

The degree of initial wasting in each patient, however, has been assessed roughly by taking the weight on admission (or after rehydration if dehydration were present) and comparing it with the weight at birth

FIG. 3.—Scatter diagram of weight gains per kg. body weight per day of twenty-six infants (Groups 1 and 3).

plus 5 oz. for each week of age, that is, the expected weight. The clinical signs of malnutrition were usually in agreement with the assessment made on weight; in a few cases they were not, and such infants were omitted from the investigation. An underweight infant must gain weight faster than the normal infant in order to catch up and reach the normal range of weight levels. Individual progress was therefore gauged by the rapidity with which this was achieved.

Fig. 1 is a comparison between the Iowa standards and the weight curves from birth of the twenty marasmic infants suffering from pyloric stenosis who made straightforward progress after operation

(Group 1). The weight of the patient at operation was always taken after dehydration had been corrected. Later, points from the weekly weight records have been graphed only at times when there was a change in rate and therefore in the slope of the line. It can be seen that pyloric obstruction was treated at an interval after birth varying between three and seventeen weeks and that many of the infants had lost, and none of them had gained, weight during this time. Subsequently, there was a considerable variation in the rate at which weight was gained, but in every case a steady increase was achieved. It will be noticed that the slope of the line (representing the rate) is often steeper than the slope of the standard curves and that the weight then begins to approach the normal. At three months of age many of the babies were still far below the standard although several weeks had usually elapsed since the time of their operation. Most of them, however, were by then gaining weight at a rate which, if continued, would enable them to reach the normal range within the next few weeks. No. 20 was an exceptional case. He had become progressively wasted until, at seventeen weeks, pyloric stenosis was diagnosed, and by this time he weighed only 50 per cent. of his expected weight by the Iowa standard. Operation was followed by the usual feeding regime for marasmic infants and excellent progress was made. At twenty-three weeks he was nearing the normal range.

Fig. 2 shows the weight curves of the fifteen infants with pyloric stenosis whose progress was retarded by infection (Group 2). In general, the course of these infants was slower than that of the patients in Group 1, but it was usually retarded for a time only, later the rate of gain becoming similar to that of the uncomplicated cases. This was to be expected since infections were often controlled within a week or two. The intake of food had sometimes to be curtailed for these babies, but the calorie intake was

TABLE 4
VARIATION IN AMOUNT OF WEIGHT GAINED PER WEEK BY INFANTS IN GROUPS 1 AND 3

Weeks		1	2	3	4	5	6
Group 1	Average weight Gain (g./week)	153	227	275	266	303	293
	Range ..	0 to +270	-28 to +455	-28 to +540	-71 to +511	+198 to +498	+128 to +455
	No. of cases ..	20	20	19	17	14	13
	Average Weight Gain (g./week)	144	196	222	238	110	280
Group 3	Range ..	-85 to +325	+85 to +270	+184 to +312	+99 to +341	+57 to +142	+156 to +425
	No. of cases ..	6	6	6	5	4	4

never reduced to 'maintenance' levels, and was increased by giving Stage II feed as soon as possible. Many of the infants continued to gain weight despite the fact that severe infections were present. One infant (No. 10) died six weeks after operation from epidemic gastro-enteritis contracted three days previously. His course after operation had been complicated by persistent vomiting, and at necropsy he was found to have a healed cerebral birth injury which might have caused this symptom and accounted for his slow progress.

Fig. 3 shows the weight gains (as g./kg./day) during each week, for the two groups of infants (1 and 3) who made straightforward progress. It will be seen that the range is wide, but that a large number of infants were gaining much more than the 7 g./kg. daily which is the average for healthy, full-term infants during the second and third months of life. The relatively higher rate of gain achieved by the marasmic infants is due partly to larger total weight gains (see fig. 1) but partly to their initially low weights. Since requirements of food are always prescribed on the basis of body-weight, however, the amount of weight which is being gained can best be related to the diet if it is expressed as g./kg./day. Fig. 3 shows that a gain of 15 g./kg./day was often achieved by patients who were fed according to the regime shown in tables 1 and 2. Amounts of nitrogen equivalent to 2-3 g. protein/kg./day must have been retained by these infants (weight gain = $\frac{1}{2}$ protein). Hence, allowing for a 50 per cent. utilization, their diet (containing about 6 g. protein/kg./day) was probably sufficient for their needs. The high content of minerals in the diet may also have contributed to these results.

Fig. 4 shows the cumulative gain in weight of the infants during the early weeks of their treatment. The weight gains of the individuals in Groups 2 and 4 (complicated cases) have been graphed to compare with the average gains of those in Groups 1 and 3 (uncomplicated cases). The range for change in weight and the average gains each week for Groups 1 and 3 are given in table 4. It can be seen that on an average the infants in Group 1 were gaining about 275 g. (10 oz.) per week from the second to the sixth week and that many were gaining considerably more than this, the maximum gain being 540 g. per week (19 oz.). The rate of gain shown in the Iowa curves during a similar age period (sixth-twelfth week) is about 235 g. per week, but healthy infants seldom gain amounts which greatly exceed this. Fig. 4 shows that the progress of some of the infants with complications (Groups 2 and 4) was similar to that of the infants in Groups 1 and 3; others gained slowly for a week or two, but later there was an increase in the rate. A few infants lost weight and, later, gained slowly for several weeks. One infant in Group 4 (No. 16) died of severe infection contracted during the neonatal period. Nevertheless, the nutrition of many of the infants in these groups was well maintained at times

when infection might have been expected to produce a steady downhill course.

Serum Protein and Haemoglobin Levels

The amounts of serum protein and haemoglobin have been found to fall in starvation and in protein depletion and to rise during periods of recovery in experimental animals (Weech, Goettsch, and Reeves, 1935; Weech, Wollstein, and Goettsch, 1937; Sabine and Schmidt, 1943; Chow, 1946) and in adult man (Mollison, 1946; Walters, Rossiter, and Lehmann, 1947). The changes in serum protein levels are due mainly to the albumin fraction. The blood volume also falls in starvation and rises in recovery and such variations in volume may mask an absolute decrease or increase in the amounts of total circulating protein and haemoglobin. Marriott (1920) and Uthman (1920) have found that the blood volume and the concentration of protein and of haemoglobin are often low in marasmic infants. Infection, if present, contributes to the production of low levels by depressing haemoglobin formation (Davidson and Fullerton, 1938; Vaughan, 1948) and plasma regeneration. Changes in the haemoglobin and serum protein levels cannot be used as a guide to the degree of depletion or to assess recovery in marasmic infants, since the normal range for both serum protein and haemoglobin levels is wide in infancy, and they are often affected by factors other than protein depletion, such as infection and changes in the blood volume.

When the present investigation was being planned it was decided to take samples of blood for serum protein and haemoglobin estimations at the outset of treatment and again at weekly intervals and to obtain them from scalp veins by venipuncture. Unfortunately it has not been possible to follow this programme systematically, but the blood of most of the patients has been examined on several occasions; exceptions were two infants in Group 1 and three infants in Group 4. The samples were usually obtained by scalp vein puncture but capillary blood from a heel-prick was occasionally used. The number of weekly levels from each case varied, depending upon the duration of in-patient treatment and upon the number of return visits. Since follow-up care usually extended over a longer period for the more severe cases, the levels for the later weeks of treatment may lie within a lower range than would have been the case if complete sampling had been achieved. A greater number of levels were estimated on the patients in Groups 2 and 4, whose progress was retarded, than on those in Groups 1 and 3 who made straightforward progress.

Serum was used for the protein estimations, haemolysed specimens being discarded. The total nitrogen was determined by micro-Kjeldahl digestion followed by nesslerization. Albumin nitrogen and non-protein nitrogen were estimated by the same method; the globulin was removed by precipitation with 22.2 per cent. sodium sulphate followed by filtration and the total protein was precipitated by

sodium tungstate and sulphuric acid. A correction was applied in calculating the total protein nitrogen and albumin nitrogen by subtracting the non-protein nitrogen. Since completing this investigation it has been found that the average of a series of results for total serum protein levels obtained by this method is lower, by approximately 0.3 g./100 ml., than the average of the same series of results obtained by the digestion of 0.1 ml. of serum followed by steam distillation and titration. Fortunately the same nesslerization technique has been employed to determine the serum protein levels

at the time when this investigation was in progress). The haemoglobin levels of normal infants have not been estimated by the same technique, but Horan (1949) has used the Haldane method to estimate the haemoglobin levels of a series of normal infants in Birmingham matching them against a standard solution by direct vision. The results obtained by this investigator have therefore been used as a standard with which to compare the levels of our patients. The curve showing the average haemoglobin levels of artificially fed infants between one and five months of age lies about 10 per cent. higher

FIG. 4a.—Cumulative weight gains of fifteen infants (Group 2) admitted with pyloric stenosis (complicated course) compared with average gain of twenty infants (Group 1) making steady progress.

FIG. 4b.—Cumulative weight gains of seventeen infants (Group 4) suffering from marasmus associated with infection compared with average gain of six infants (Group 3) without infection.

in a series of normal infants (Poyner-Wall and Finch, 1949) and the results of this investigation have been used as a standard with which to compare the levels of our patients.

Haemoglobin was estimated in the Evelyn photoelectric colorimeter against a standard curve based on Van Slyke's oxygen capacity determination using the commonly accepted value of 1.34 ml. of oxygen/g. haemoglobin (100 per cent. = 13.8 g. haemoglobin, the Haldane standard 'normal' level

than that obtained by Mackay (1933) for London infants using the same method for the estimations.

Serum protein levels. Fig. 5 shows the serum protein levels of the four groups of infants compared with the average level for normal infants of similar ages, that is, one to five months (Poyner-Wall et al., 1949). The levels of the infants who made steady progress (Groups 1 and 3) have been graphed separately from those whose course was retarded by infection (Groups 2 and 4). Both sections of the

diagram show that during the first two weeks of treatment a larger number of the levels were below than were above the average line for normal full term infants. After four weeks, however, a greater proportion of the levels reached a value above the line for the infants in Groups 1 and 3, while they continued to be below it for those in Groups 2 and 4, whose progress was complicated by infection. The levels show a wide scatter and no close relationship was found between them and the severity of the wasting in the different patients.

The protein levels of our patients were higher

shown in fig. 6. The initial serum protein concentrations within a few days of operation were found to be higher than those one to three weeks later, whereas subsequent values showed an increase. This sequence or part of it was found in fifteen out of the sixteen infants in Group 1 whose levels were estimated regularly. The same changes occurred in the levels of a number of the infants in the other groups but not so consistently. The cases within Group 1 were more alike clinically than were those in the other groups, and this may explain why the sequence of changes in their serum protein levels

FIG. 5.—Serum protein levels of marasmic infants (a, Groups 1 and 3; b, Groups 2 and 4) compared with average serum protein levels of normal infants in same age group, 1-5 months (Poyner-Wall and Finch, 1949).

than those for marasmic infants recorded by other workers (Utheim, 1920), and the uniformly high protein diet used in this investigation may account for this difference. Hypoproteinaemia was more often found amongst the group of marasmic infants who were the subjects for the preliminary tests with casein hydrolysate, and these patients were usually given much less protein than the infants in the later systematic investigation.

The results of serial estimations of the serum protein levels in individual infants often showed unexplained fluctuations from week to week. A pattern was discernible, however, in the recovery phase of many of the infants in Group 1, and it is

was more uniform. The pattern is similar to the one described during recovery from protein depletion in rats (Cannon, Humphreys, Wissler, and Frazier, 1944) and in adult man (Walters et al., 1947). It was then shown to be due to an initial rise in the blood volume which takes place at a faster rate than the increase in the amount of total circulating protein. The serum albumin levels obtained from the same samples of blood as were used for the total serum protein levels are also shown in fig. 6. It will be seen that they usually changed in the same direction as the total protein levels and that the changes in albumin were then mainly responsible for the fall and rise in the total concentrations.

This was also found to be the case in animals and adults suffering from malnutrition (Weech et al., 1935; Rossiter, 1946). In some of our patients, however, the albumin concentration changed in the opposite direction from the total protein; no explanation is offered for these differences in the fractionation of albumin and globulin.

standard, it would not have been apparent. This finding is in accord with the results for the serum protein levels. Only three cases of severe anaemia (haemoglobin below 60 per cent.) occurred in the whole series of infants, and infection was present in two of them. These patients were among those who received transfusions. A higher incidence of

FIG. 6.—Changes in serum protein levels of sixteen infants in Group 1 during convalescence following operation for pyloric stenosis (steady progress).

Haemoglobin levels. Fig. 7 shows the haemoglobin levels of the four groups of infants compared with the average normal levels of artificially fed infants of similar ages, that is, one to five months (Horan, 1949). Since the normal haemoglobin curve is falling steeply during this period, the levels have been graphed as percentages above or below the standard levels. In this way they are shown in relation to the course of treatment. The levels of the premature infants are distinguished by (P) and those of the infants who received transfusions by (T). None of the levels estimated subsequent to transfusion has been recorded. The levels of the infants who made steady progress, Groups 1 and 3, have been separated from those in Groups 2 and 4 whose course was retarded by infection in sections (a) and (b) of Fig. 7. It may be seen that throughout the period of observation a larger number of the levels were below than were above the average for normal full term infants. The tendency to anaemia is slight, however, and if a lower curve (Mackay, 1933) had been used as the

anaemia might have been expected from descriptions in the literature of marasmic infants and, again, the food which our patients were receiving may explain the results.

Non-protein Nitrogen Levels

The non-protein nitrogen levels were estimated regularly on the same samples of blood as were used for serum protein and haemoglobin levels. The results show that the levels usually varied between 20 and 50 mg./100 ml. but occasionally high levels of the order of 80-90 mg./100 ml. were obtained. None of these was associated with a low serum bicarbonate level which would have indicated acidosis due to renal insufficiency. They were judged to be due to a high urea production from metabolism of the protein in the diet since the blood urea levels were also high. The levels tended to fall, and usually lay within the normal range if the intake of total calories was increased by the addition of carbohydrate.

Discussion

The process of recovery in wasted infants has not to our knowledge been studied fully, nor have reports of the progress of series similar to the present one been found in the literature. The early post-operative progress of infants with pyloric stenosis has been studied in relation to diet (Levi,

methods for controlling infection as well as to better nutrition during the period of recovery.

No claim is made that the patients whose progress has been described were receiving optimum diets for their requirements. It is possible that other sources of protein besides casein might be used with advantage either in their natural or partially digested

FIG. 7.—Haemoglobin levels of marasmic infants (a, Groups 1 and 3; b, Groups 2 and 4) compared with average levels for normal artificially fed infants (Horan, 1949). Each estimation has been expressed as a percentage above or below the average level for age.

1941), but the course of those suffering from marasmus was not separated from that of the babies whose obstruction was relieved before wasting became a prominent symptom. It has been asserted that gain in weight is often delayed for a considerable time in severely wasted infants (Utheim, 1920; Parsons, 1924). Most of the infants in the present investigation started to gain weight during the first week of treatment, and progress, even in those with definite signs of infection, was usually well maintained. Serious or chronic infection, however, was associated with an unsatisfactory course, as in case No. 4 (Group 4) who was suffering from multiple osteomyelitis. The free use of sulphadiazine and penicillin has undoubtedly contributed much to the good results which have been obtained. The relatively low incidence of hypoproteinaemia and of severe anaemia may also be due partly to these

state. It has been shown, for example, that protein regeneration and haemoglobin production are stimulated by the administration of plasma, meat, and liver especially (Pommerenke, Slavin, Kariher and Whipple, 1935). The effects of these substances may be due to their amino-acid composition or to other less specific factors.

Many of the patients were discharged from hospital while they were still suffering from a severe degree of undernutrition, and our attention has been drawn to the need for a long period of after-care for such infants in order that they may reach a state of normal nutrition as soon as possible. The 4.5 oz. gain per week which is commonly accepted as adequate is insufficient to enable them to attain the normal weight range for their age and often a better rate can be achieved by improving the diet. Care should be taken also to protect marasmic infants

FIG. 8a.

FIG. 8b.

FIG. 8c.

FIG. 8a.—Case No. 19 R.H. (Group 1). Male infant aged four weeks, birth weight 7 lb. 3 oz. History of vomiting for ten days. Weight at operation 6 lb., i.e. 71 per cent. of expected weight. Post-operation feeding for marasmic infants with pyloric stenosis (table 2) followed closely. Patient discharged sixteen days after operation weighing 6 lb. 12½ oz. He was receiving 21 oz. per day of stage III feed (table 1) supplying 420 calories and 21 g. protein. At return visit eight days later weighed 7 lb. 10½ oz. and was receiving 24 oz. per day supplying 480 calories and 24 g. protein. The first photograph (fig. 8a) was taken before, and the second (fig. 8b) twenty-four days after operation. Fig. 8c shows weight gain, and serum protein and haemoglobin levels during same period.

from contact with infection; they are not only extremely susceptible but withstand it very badly. This may be partly due to a poor immunological response such as is known to be associated with protein depletion in animals (Cannon, Chase, and Wissler, 1943; Wissler, Wooldridge, Steffee Jr., and Cannon, 1946).

Studies of the metabolism of sick and wasted infants should be planned in order to obtain greater understanding of their requirements, particularly of nitrogenous foods. Further knowledge of their needs could now be readily applied, since digests of protein from various sources are available and could be given at an early stage of convalescence with little risk of intolerance by the alimentary tract.

Summary

Observations have been made on seventy-nine infants suffering from marasmus who weighed 80 per cent. or less of the expected weight before treatment.

The cause of the wasting was diagnosed and treated and efforts were made to improve nutrition without delay. Hydrolysed casein was used to augment the protein intake in the early stages of graded feeding, and later undiluted cows' milk mixtures were substituted. The feeds were arranged to provide about 120 calories and 6 g. of protein/kg./day throughout treatment.

Progress was assessed by the rate of gain in weight and recovery appeared to be made earlier and to proceed more regularly than before. If infection was present it sometimes did and sometimes did not retard the rate of recovery.

The serum protein and haemoglobin levels were estimated at weekly intervals for the periods during which the patients remained under hospital care. The changes in the serum protein levels were irregular but were sometimes found to be similar to those which have been described for animals and for adult man during periods of recovery from starvation and protein depletion. Severe hypoproteinaemia and anaemia were seldom found.

Many weeks may elapse before a wasted infant attains a good nutritional status. During this time special care is needed to ensure that he receives an optimum diet until his weight reaches the normal range for his age, and to prevent exposure to infection.

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Correction:—Messrs. Wm. R. Warner, London, point out that 'beminal' which was referred to on p. 169 of the September issue is not marketed by their American company, Warner Bros., U.S.A., but by Ayerst, McKenna and Harrison of Montreal.