Role of the Adrenal Cortical System in the Response of Children to Severe Protein Malnutrition

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KWASHIORKOR and marasmus are two contrasting clinical forms of severe malnutrition in children in technically underdeveloped areas. Among the outstanding clinical, biochemical and histopathologic characteristics of kwashiorkor are edema, severe hypoalbuminemia and fatty liver; neither edema nor fatty liver are found in marasmus and the albumin is not reduced much below normal values.[1]

The child with marasmus appears to be one whose synthesis of essential proteins, particularly those formed in the liver, has not suffered; he defends himself well through consumption of his own protein "reserves," principally muscle, and reaches a terminal state only gradually. On the other hand, in the child with kwashiorkor, some mechanism seems to have failed acutely with resulting physiopathologic alteration of a serious nature. Imbalances between anabolism and catabolism of serum albumin and of some other fundamental protein moieties, e.g., enzymes, develop rapidly in the acute phase of kwashiorkor, and are readily reversible only with appropriate therapy.

On the basis of epidemiologic observations, the appearance of one or the other of these two syndromes has been attributed to differences in the ratio of calories to protein in the diet. If the diet is poor in protein, both quantitatively and qualitatively, but has a relative excess of calories, kwashiorkor develops; if the diet is proportionally insufficient in both protein and calories, the result is marasmus.[1] This, however, does not explain the mechanism responsible for the differences in the physiopathology of kwashiorkor and marasmus. Moreover, the typical signs of kwashiorkor may be superimposed on a considerable degree of wasting and muscular loss. This condition is very frequent and is referred to as "marasmic kwashiorkor."

This study explores metabolic mechanisms which may determine which of the two clinical conditions develops in a malnourished child. When our attention was directed toward possible alterations in the endocrine system, the adrenal cortical system was selected for initial studies because of (1) its direct role in the ability of the organism to react to stress, since it is obvious that severe malnutrition is itself a basic stress, and (2) the presence of edema and electrolyte imbalance,[2–8] changes which are known to depend in part on adrenal cortex function. The endocrine system has been studied in adults with chronic malnutrition[9,10] but reports suggesting endocrine alterations in malnourished children are very limited.[11,12]

Endocrinologic observations in a group of children with either acute kwashiorkor or marasmus, and experiments with protein malnourished rats submitted to specific hormone administration, are presented.

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TABLE I
Characteristics of the Patients Studied

Group	Patients (no.)	Age (mo.)		Weight (kg.) Mean ± S.E.*	Serum Proteins (gm./100 ml.) Mean ± S.E.*	Edema
		Mean	Range			
Kwashiorkor	6	41.0	18–60	9.1 ± 1.65	3.84 ± 0.26	Present
Marasmus	5	5.6	2.5–12	3.2 ± 0.52	5.33 ± 0.32	Absent

* Standard error.

EXPERIMENTAL DATA

Observations in Malnourished Children

Subjects. Six children with kwashiorkor, and five with marasmus were chosen by clinical criteria which have been discussed elsewhere.[1] Edema was present in all the patients with kwashiorkor but not in any of those with marasmus. Some characteristics of these subjects are given in Table I.

Experimental Plan. Children with acute disease were admitted to the metabolic ward and given orally an electrolyte solution† during the first eighteen hours. A therapeutic diet of whole or half skim milk was then introduced and other foods gradually added as described previously.[13] A 10 ml. fasting venous blood sample was taken in the morning of the day following admission, 1 ml. of which was added to an anticoagulant to permit counting of eosinophils. The rest was allowed to clot and the serum separated for biochemical determinations. The child was kept in a bed equipped for quantitative urine collections and urine was collected for twelve hours in most cases and for twenty-four hours in some instances. All data on urinary excretions were calculated to twenty-four–hour periods. During collections the urine specimens were kept on ice without preservative.

Twenty-four hours after the first blood sample, an intramuscular injection of 10 I.U. of ACTH† was given and a twelve- or twenty-four–hour urinary collection was repeated. Six hours after the dose of ACTH another blood sample was taken. During the second week of hospitalization, when the patient had made major progress toward recovery, blood and urine were collected before and after stimulation with ACTH in the same manner. This procedure was repeated once more about two months later when the child was considered clinically recovered.

Studies with Rats

Material. Three separate experiments were carried out with Sprague-Dawley rats of both sexes.

Experiment 1: As a preliminary experiment, thirty rats were taken after weaning and fed Purina Laboratory Chow for one week. They were then given an experimental diet with the following composition in grams per 100 grams: ground yellow corn 61.8, corn starch 15.3, alphacel 15.3, cottonseed oil 3.5, Hegsted Mineral Mixture‡ 2.7, cod liver oil§ 1.4; vitamins were added as follows, in milligrams per 100 grams of diet: thiamine hydrochloride 3, riboflavin 3, nicotinic acid 5, calcium pantothenate 10, pyridoxine 3, biotin 0.01, folic acid 0.02, vitamin B_{12} 0.002, inositol 40, choline chloride 150, para-aminobenzoic acid 30 and menadione 1. This diet was deficient in protein both qualitatively and quantitatively, but contained all other known essential nutrients for the rat in sufficient amounts.

After twenty-one days on this diet, six animals were sacrificed following light ether anesthesia. Blood was collected and the serum separated by centrifugation for total protein and albumin determinations. The liver was observed macroscopically and a

* Lytren,® Mead Johnson & Company, Indiana.
† ACTHAR® Gel, Armour Laboratories, Illinois.
‡ Nutritional Biochemical Corp., Cleveland, Ohio.
§ 1,800 I.U. vitamin A and 200 I.U. vitamin D per gram.

section fixed in 10 per cent formaldehyde for histopathologic examination.

The remaining twenty-four rats were divided into four groups of six animals for treatment as follows: group I (control), 0.5 ml. of 0.85 per cent sodium chloride solution administered subcutaneously; group II, 3.12 mg. of cortisone acetate in aqueous suspension given subcutaneously; group III, 2 I.U. of ACTH administered subcutaneously; and group IV, 0.5 mg. of desoxycorticosterone acetate (DOCA®) in oil solution given intramuscularly. The injections were given daily to each animal for twenty-one days. At the end of this period all the rats were sacrificed and the blood and liver were sampled as before. The weights of the animals were determined throughout the experimental period.

Experiment 2: The general planning was similar to that of experiment 1 except that the rats were placed on the experimental protein deficient diet immediately after weaning. The animals were maintained on this diet throughout the experiment. After twenty-one days, six animals were assigned randomly to a "basal group" which was sacrificed to obtain pretreatment information. The remaining fifty-four rats were distributed among three groups of eighteen rats each, with each group balanced for weight and sex as nearly as possible.

The following treatments were given daily for twenty-one days: group I(control), 0.125 ml. of 0.85 per cent sodium chloride solution given subcutaneously; group II, 3.12 mg. of cortisone acetate in 0.125 ml. aqueous suspension administered subcutaneously; and group III, 1 mg. of DOCA in 0.2 ml. of oil given intramuscularly. The experimental plan called for sacrificing six animals from each group weekly. Deviations from this sampling plan were due to the deaths of two rats each in groups II and III, and the sacrifice of only five control animals at the end of the second week.

A blood sample was collected from each rat and the serum separated for measurement of total proteins, electrophoretic protein fractions and urea nitrogen. The liver was weighed and a fragment was fixed in formaldehyde for histopathologic studies. About 500 mg. of liver tissue were homogenized in ice cold distilled water to a final concentration of 1:10 in a Potter-Elvehjem glass homogenizer to determine liver moisture, protein and fat content.

The left psoas muscle was dissected out and weighed; a fragment of it was fixed in formaldehyde for histopathologic examination and another homogenized in the same way as the liver for protein determination. The viscera were then entirely removed and the water content of the carcass was determined. The animals were weighed throughout the entire experimental period, and data on food consumption were collected during a three-day period in the third week of treatment.

Experiment 3: After weaning, twenty-four rats were fed Purina Laboratory Chow for twenty-one days, and at the end of this period, six were sacrificed for the identical study described in experiment 2. The eighteen remaining animals were divided into the same three groups of six rats each. They also received the same treatments as in experiment 2 while continuing to be fed Purina Laboratory Chow for another twenty-one-day period. All the animals were sacrificed and studied as described before.

METHODS

The following methods were used: Eosinophil counting, Speirs;[14] 17-hydroxysteroids in urine, Reddy;[15] 17-ketosteroids in urine, Drekter et al;[16] serum total proteins, Lowry and Hunter;[17] serum albumin, Debro et al;[18] electrophoretic analysis, by paper electrophoresis in barbital acetate buffer pH 8.6 at an ionic strength 0.075 using 110 volts for sixteen hours with colorimetric estimation after amido-black staining and elution in 0.01 N sodium hydroxide; urea nitrogen in serum, by nesslerization after incubation with urease and precipitation of proteins with tungstic acid; total proteins in liver and muscle tissue, using the phenol reagent of Folin-Ciocalteu according to Lowry et al.;[19] moisture, drying-oven at 100°c. to constant weight; liver fat, measured in an extract of a 1:10 homogenate with Bloor's mixture by the oxidation method of Bragdon.[20]

TABLE II

Endocrine Findings in Children Suffering from Kwashiorkor and Marasmus Before and After Administration of ACTH

Test	Condition	Number of Patients			A = Initial*		B = After 2 Weeks Therapy*		C = After 8 Weeks Therapy*	
		A	B	C	Before ACTH	After ACTH	Before ACTH	After ACTH	Before ACTH	After ACTH
17-hydroxysteroids (mg./24 hr.)	Kwashiorkor	6	6	5	1.0 ± 0.27	4.60 ± 1.18	1.0 ± 0.46	3.8 ± 0.60	2.0 ± 0.71	4.1 ± 0.52
	Marasmus	5	5	3	3.3 ± 0.65	3.74 ± 0.56	1.3 ± 0.32	3.2 ± 0.49	1.4 ± 0.80	2.6 ± 0.37
17-ketosteroids (mg./24 hr.)	Kwashiorkor	6	6	5	0.5 ± 0.20	2.73 ± 3.80	1.1 ± 0.90	1.4 ± 1.08	0.6 ± 0.41	1.2 ± 0.26
	Marasmus	5	5	3	0.8 ± 0.18	1.04 ± 0.19	0.9 ± 0.42	0.6 ± 0.31	0.4 ± 0.40	0.6 ± 0.58
Eosinophil† count (per cu. mm.)	Kwashiorkor	4	6	6	82 (56–100)	...	438 (133–872)	...	631 (144–1100)	...
	Marasmus	5	5	3	9 (0–22)	...	83 (122–155)	...	119 (17–206)	...

NOTE: The twenty-four hour urinary excretions of steroids are in absolute terms and not per square meter of body surface because, due to an oversight, no accurate record of the children's height was taken. It should be emphasized, however, that since the children with marasmus were much younger and weighed much less than those with kwashiorkor, expressing the data per unit of body surface would have indicated even more dramatically the higher steroid excretions of the patients with marasmus.

* Mean ± standard error.

† Range of eosinophil counts is given in parenthesis below the mean.

RESULTS

Children. Table II gives the results of the determination of urinary excretion of steroids and the eosinophil counts of the children with kwashiorkor and marasmus. The eosinophil count was much lower in all the children with marasmus on admission, and despite their younger age they excreted significantly more 17-hydroxysteroids than the children with kwashiorkor. Both of these indices suggest an overactive glucocorticoid function in marasmus. The average 17-ketosteroid excretion was not significantly different in the children with kwashiorkor compared to those with marasmus.

After two weeks of treatment the difference in values for 17-hydroxysteroids in the two conditions was less, and after eight weeks the relationships were reversed. The significantly lower eosinophil counts in children with marasmus than in those with kwashiorkor at admission were observed also upon each subsequent examination although the values increased with treatment in both groups. On admission, the response in 17-hydroxysteroid excretion to ACTH was relatively and absolutely much more marked in the patients with kwashiorkor who also had significantly lower excretions before stimulation with ACTH. No response was observed in three of the children with marasmus and a slight response in two, suggesting an overstimulated gland in this condition even before the administration of ACTH. At the second and eighth weeks, differences in response between children with marasmus and those with kwashiorkor were no longer significant.

On admission, the 17-ketosteroids of children with kwashiorkor increased significantly after the administration of ACTH but the response in those with marasmus was relatively small and not significant. At the end of the second and eighth weeks differences in this measurement were less marked.

Rats. Experiment 1: The results of the first rat experiment are given in Table III. After three weeks on the "poor protein diet," serum proteins and albumin values were low. The administration of cortisone for three weeks resulted in a marked rise in the serum total proteins, due entirely to an increase in the albumin concentration. This finding contrasted with those for the other three groups, in which the albumin even decreased from the pretreatment value; the globulins on the other hand, had a tendency to increase, particularly in the groups treated with DOCA and ACTH.

TABLE III

Serum, Liver and Weight Findings in Protein Deficient Rats Given Adrenal Cortical Hormones or ACTH (Six Rats per Group)

Test	Pretreatment	Three Weeks Treatment			
		Sodium Chloride	Cortisone	ACTH	DOCA
Serum*† (gm./100 ml.)					
Total proteins.....	4.61 ± 0.16	5.10 ± 0.18	6.11 ± 0.10	5.24 ± 0.05	5.26 ± 0.10
Albumin.....	2.45 ± 0.17	2.29 ± 0.08	3.78 ± 0.09	2.14 ± 0.06	2.21 ± 0.07
Globulin.....	2.16 ± 0.09	2.80 ± 0.14	2.33 ± 0.07	3.09 ± 0.07	3.05 ± 0.10
Liver	(+)	(++)	(0)	(+)	(+++)
Fat infiltration (histopathologic evaluation with Sudan IV)	(+++)	(+)	(±)	(+)	(+++)
	(++)	(+++)	(±)	(±)	(+)
	(++)	(++)	(++)	(+)	(++)
	(++)	(+)	(+)	(+)	(+)
	(±)	(+)	(±)	(+)	(++)
Weight (gm.)†					
Initial.....	...	79.7 ± 3.91	77.3 ± 5.43	81.7 ± 3.77	73.4 ± 4.13
After therapy.....	...	107.0 ± 5.20	77.7 ± 5.64	106.7 ± 6.45	85.0 ± 7.20
Net gain.....	...	27.3 ± 4.38	0.4 ± 3.57	25.0 ± 4.81	11.6 ± 3.89

* Five rats only in pretreatment group.
† Mean ± standard error.

TABLE IV

Food Consumption, Body and Muscle Weights in Protein-Deficient Rats Treated with Cortisone and DOCA*

Treatment	Food Consumption (3 days total)	Body Weight (gm.)				Carcass Moisture† (gm./100 gm.)	Psoas Muscle Weight†	
		Before Therapy	1 Week	2 Weeks	3 Weeks		mg.	Per gm. of Body Weight
Sodium chloride..	23.4 ± 1.86	49.1 ± 2.66	53.6 ± 2.48	55.7 ± 2.69	57.8 ± 2.71	60.2 ± 0.61	915 ± 39.0	15.9 ± 0.61
Cortisone..	24.0 ± 1.76	48.0 ± 3.85	51.8 ± 4.92	50.2 ± 4.99	45.0 ± 4.54	62.9 ± 1.46	439 ± 67.7	9.6 ± 0.58
DOCA.....	23.4 ± 2.73	51.7 ± 1.60	56.0 ± 2.22	61.0 ± 2.31	65.3 ± 3.45	58.5 ± 0.93	825 ± 80.4	12.7 ± 0.90

* All values are mean ± standard error. For number of animals in each case see Table V.
† After three weeks of treatment.

TABLE V

Effect of Cortisone and DOCA on the Serum Proteins (gm./100 ml.) and the Serum Urea Nitrogen (mg./100 ml.) of Protein-Deficient Rats*

Treatment	Weeks of treatment	No. of Rats	Total Serum Protein†	Serum Albumin	Serum α-Globulin	Serum β-globulin	Serum γ-globulin	Serum Urea Nitrogen‡
Sodium chloride	1	6	4.30 ± 0.11	2.39 ± 0.13	1.05 ± 0.03	0.57 ± 0.04	0.35 ± 0.03	22.3 ± 1.15
	2	5	4.39 ± 0.12	2.23 ± 0.10	1.17 ± 0.04	0.67 ± 0.03	0.31 ± 0.03	24.3 ± 0.41
	3	7	4.48 ± 0.07	2.35 ± 0.13	1.14 ± 0.04	0.62 ± 0.04	0.36 ± 0.07	28.4 ± 1.27
Cortisone	1	6	5.41 ± 0.17	3.63 ± 0.18	1.02 ± 0.04	0.53 ± 0.06	0.22 ± 0.02	13.4 ± 0.35
	2	5	5.36 ± 0.20	3.45 ± 0.24	0.66 ± 0.23	0.72 ± 0.04	0.14 ± 0.01	17.0 ± 0.74
	3	5	4.95 ± 0.26	3.15 ± 0.26	0.96 ± 0.08	0.67 ± 0.06	0.16 ± 0.02	25.9 ± 4.91
DOCA	1	6	3.95 ± 0.09	2.08 ± 0.07	0.96 ± 0.05	0.69 ± 0.04	0.22 ± 0.02	23.8 ± 1.50
	2	4	3.70 ± 0.34	1.67 ± 0.52	1.01 ± 0.03	0.83 ± 0.06	0.20 ± 0.03	28.2 ± 7.25
	3	6	4.81 ± 0.20	2.10 ± 0.16	1.32 ± 0.11	0.80 ± 0.06	0.63 ± 0.13	29.0 ± 3.71

* All values are mean ± standard error.
† Before treatment six rats averaged 4.63 ± 0.15 gm./100 ml. total serum protein after five weeks on the basal diet.
‡ Pretreatment value for six rats: 19.4 ± 1.51.

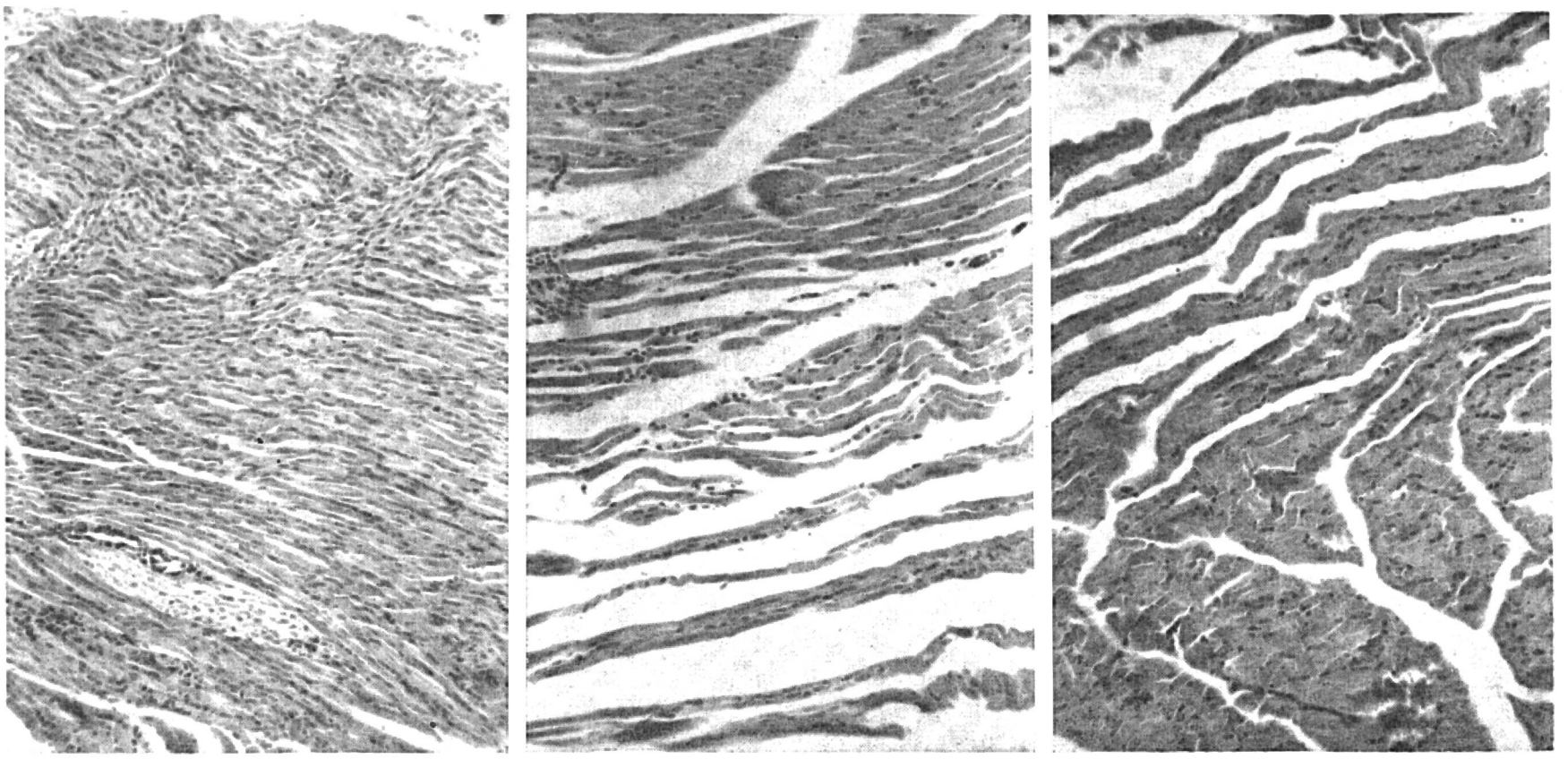

FIG. 1. Rat psoas muscle before administration of cortisone (*left*), at the second week of treatment (*middle*), and at the end of the third week of cortisone therapy (*right*). Hematoxylin and eosin stain, magnification ×100.

The results of the histologic appraisal of the liver indicate a clear-cut effect of cortisone reduction of the initial fat infiltration observed in the pretreatment group. This effect was similarly shown in the group given ACTH in contrast with the albumin regeneration effect which only cortisone produced. The animals treated with sodium chloride, and particularly those treated with DOCA, showed no decrease in hepatic fat content. Animals treated with cortisone gain practically no weight as an average, while those treated with sodium chloride and ACTH gain most.

Experiment 2: The results of the second experiment with protein deficient rats, are illustrated in Tables IV through VI. Table IV shows that the rats receiving cortisone failed to grow, while those given injections of sodium chloride solution or DOCA, gained some weight, although slowly due to the very inadequate protein intake. These results are in agreement with those of experiment 1. Carcass moisture was essentially the same in all groups.

The final weights of the psoas muscle in the three groups are entirely different and indicate a marked degree of muscle tissue wasting in the cortisone group. This is also illustrated by the much lower muscle body weight ratio shown in the last column of Table IV and by the histologic appearance of the muscle fibers (Fig. 1). At the third week of treatment the protein content of the muscle was 17 per cent for the group receiving sodium chloride, 17 per cent for the group receiving cortisone and 18 per cent for the group receiving DOCA.

The amount of food consumed was the same in the three groups. More complete data on food consumption have been collected in a subsequent experiment, during twelve-day periods with thirteen animals in each group, without finding any differences between groups.

The effects of the hormone treatments on the concentrations of serum total protein and its electrophoretic fractions and on serum urea are presented in Table V. Marked elevation in albumin by cortisone, as found in the previous experiment, was again observed. The effects on the globulins were less marked than in albumin although a significant lowering of the gamma globulin by cortisone was evident. It should be noted that at the end of the third week the serum total protein level of the group receiving DOCA approached that of the animals treated with cortisone. Nevertheless, the distribution of the protein fractions was contrasting in the two groups, the group receiving cortisone having an albumin:globulin ratio of 1:8 and the group

TABLE VI
Effect of Cortisone and DOCA on Liver Weight, Moisture, Protein and Fat
(Three Weeks of Treatment)*

Treatment	Weeks of Treatment	No. of Rats	Liver Weight (gm./kg. body weight)	Moisture (gm./100 gm.)	Protein (gm./100 gm.)	Fat (gm./100 gm.)
Pretreatment	0	6	47.9 ± 1.35	69.4 ± 0.59	15.8 ± 0.50	13.6 ± 1.23
Sodium chloride	1	6	47.3 ± 1.23	69.7 ± 0.30	15.2 ± 0.26	14.2 ± 1.28
	2	5	53.3 ± 1.62	69.2 ± 0.95	13.9 ± 0.25	12.4 ± 1.07
	3	6	56.3 ± 3.10	72.4 ± 0.94	14.5 ± 0.36	8.9 ± 1.08
Cortisone	1	6	67.9 ± 3.24	69.1 ± 0.63	16.8 ± 0.54	10.2 ± 0.63
	2	5	63.9 ± 2.16	69.9 ± 0.43	17.2 ± 0.31	9.7 ± 0.42
	3	5	62.8 ± 3.05	72.1 ± 0.37	19.3 ± 0.64	7.6 ± 0.64
DOCA	1	6	55.4 ± 1.64	70.1 ± 0.23	14.8 ± 0.32	13.4 ± 0.86
	2	4	58.8 ± 6.33	71.8 ± 3.79	13.1 ± 0.54	12.5 ± 2.72
	3	6	57.1 ± 2.63	71.8 ± 0.81	14.4 ± 0.56	10.3 ± 0.88

* All values are mean ± standard error.

receiving DOCA, 0:8. The same tendency, and to almost the same degree, was observed in experiment 1. The concentration of urea nitrogen in serum was significantly depressed at the end of the first week of cortisone treatment; this very significant effect became less marked in the two subsequent weeks.

The results of the cortisone and desoxycorticosterone treatments on the liver are shown in Table VI. Both the weight of the liver per unit of body weight and the hepatic protein concentration were higher in the rats receiving cortisone as compared with those treated with sodium chloride or DOCA. The amount of fat in the liver was less in the animals treated with cortisone than in the other two groups; while the water content of hepatic tissue was essentially the same in all groups.

Experiment 3: The results of this experiment are presented in Table VII. The administration of cortisone and DOCA to the well nourished rats did not cause the effects observed in protein-deficient animals. At about forty days of age the weight of these rats was around 200 gm. compared with an average weight of about 40 to 50 gm. for the malnourished rats of experiment 2. No significant differences in any of the other biochemical or physical measurements resulted from any of the three treatments, sodium chloride, cortisone and DOCA.

TABLE
Findings in Well
(Six Rats

Group	Weight Gain (gm.)	Total Serum Protein (gm./100 ml.)	Serum Albumin (gm./100 ml.)	Serum Globulin (gm./100 ml.)
Pretreatment	†	5.41 ± 0.05	3.37 ± 0.05	2.04 ± 0.03
Sodium chloride, third week	88.0 ± 13.25	5.72 ± 0.06	3.56 ± 0.11	2.17 ± 0.13
Cortisone, third week	42.0 ± 3.48	6.24 ± 0.12	3.51 ± 0.12	2.73 ± 0.04
DOCA, third week	63.0 ± 3.70	5.69 ± 0.11	3.33 ± 0.07	2.36 ± 0.10

* All values are mean ± standard error.

COMMENTS

Nutriture does not depend on the nutrient content of the diet alone; the response of the organism to specific dietary situations is of utmost importance, and the endocrine system plays a fundamental role in the processes of distribution and assimilation of food within the body.

Our observations in malnourished children suggest that patients with marasmus have a very high glucocorticoid hormone activity while those with kwashiorkor have a low one. From the reaction of children with kwashiorkor to the administration of ACTH, it appears that their reduced glucocorticoid activity was not due to primary inability of the adrenal gland to respond.

The studies with experimental animals reported here were designed to provide more evidence on this point. The low-protein corn diet was obviously insufficient for normal growth of the rats and its amino acid deficiencies were similar to those in the diets of malnourished children in Central America. Under these conditions, cortisone was administered in order to simulate the hyperglucocorticoid activity found in the children with marasmus, and ACTH was given to obtain information about capacity of the adrenal to respond. There is evidence that the secretion of minerocorticoids continues at normal or even increased rates after hypophysectomy.[21] If this mechanism were operating in the children with kwashiorkor, it might furnish an explanation for the universal finding of edema in patients with this syndrome. The administration of DOCA to some of the rats was based on this hypothesis.

The effects of cortisone administration conform generally to the results of other investigators,[22] that is, a loss of muscle accompanied by an increase in nitrogen content of the liver. Our data demonstrate that this reciprocal relationship between protein metabolism in muscle and in liver also operates with a very high degree of efficiency in the severely protein-deficient animal. The histopathologic and the biochemical data show that *the administration of cortisone results in a complete protection from the degenerative changes due to the limiting nutritional condition applied.*

The demonstration that an efficient regeneration of plasma albumin occurred in the animals treated with cortisone may be of great significance. This effect was very rapid; a week of treatment was sufficient to produce maximum differences which persisted throughout the period of observation between the group treated with sodium chloride and the group treated with cortisone. The hepatic nitrogen increased progressively in three weeks to the level of well nourished animals. Although observations of less than three weeks were not made, the adequately nourished rats showed no evidence at the end of the third week of any sustained effect of the administration of cortisone.

These contrasting metabolic effects of cortisone on muscle and viscera protein are accompanied under ordinary nutritional conditions by an over-all increase in urea production. In this sense the much lower concentrations

VII
Nourished Rats
per Group)*

Serum Urea Nitrogen (mg./100 ml.)	Carcass Moisture (gm./100 gm.)	Liver Weight (gm./kg. body weight)	Liver Moisture (gm./100 gm.)	Liver Protein (gm./100 gm.)
20.7 ± 0.82	68.9 ± 0.36	56.3 ± 1.67	71.0 ± 0.53	19.5 ± 0.25
29.4 ± 2.49	66.1 ± 0.14	51.0 ± 3.57	74.0 ± 1.62	19.3 ± 0.91
28.1 ± 0.59	66.0 ± 0.86	51.7 ± 1.22	72.5 ± 0.24	19.8 ± 0.49
28.8 ± 1.08	65.3 ± 0.83	58.3 ± 2.63	74.7 ± 0.34	17.8 ± 0.50

† Initial average weight for all groups (eighteen rats): 138.0 ± 6.35.

of serum urea found in the protein-deficient rats receiving cortisone, particularly at the end of one week of treatment are contrary to expectations. They suggest that the process of reutilization of amino acid nitrogen in these protein-deficient organisms includes an adaptive decrease in deamination.

By analogy with the term gluconeogenesis, we may refer to the synthesis of liver protein and serum albumin from muscle amino acids as "proteoneogenesis." The evidence presented indicates that the relative extent to which gluconeogenesis or proteoneogenesis occurs in an animal under cortisone administration or endogenous glucocorticoid production will be influenced by the state of protein nutrition; the balance will be in favor of gluconeogenesis in the adequately nourished organism and in favor of proteoneogenesis in the protein-depleted animal.

The lower fatty infiltration of the liver of the rats treated with cortisone, evidenced by macroscopic, histopathologic and biochemical examination, suggests that the malnourished organism whose glucocorticoid activity allows for a reutilization of amino acids for resynthesis of proteins and not as energy sources, fills its basic energy needs by metabolizing fat. This would explain the lower fat content of the rats treated with cortisone.

Some of the tendencies shown by the rats treated with DOCA contrast with the changes produced by the administration of cortisone. Compared with the values in the control animals, plasma albumin concentrations and liver fat deviated in opposite directions in these two groups. The plasma globulins in both rat experiments were higher in the group given DOCA than in the control group, although DOCA treatment did not seem to influence other characteristics appreciably. It must be emphasized that the rats under experimentation had their adrenal glands intact so that their glucocorticoid production, although possibly reduced, may have been confusing the response. Experiments with adrenolectomized animals are now in progress.

The underlying similarity between the child with marasmus and the deficient rat receiving cortisone is a severe malnutrition accompanied by evidence of hyperglucocorticoid activity. They have the following important consequences: (1) a high degree of muscle wasting, (2) a protection against hypoalbuminemia even under conditions of severely inadequate protein intake, (3) a liver of normal appearance both macroscopically and microscopically with no marked tendency to fatty infiltration and a normal protein content. In the protein-deficient rats treated with DOCA, and to a slightly lesser extent in the control animals given sodium chloride, two characteristics found in children with kwashiorkor were observed: (1) a reduction in the concentration of plasma albumin and total proteins, and (2) fatty infiltration of the liver. The implications of these results for therapy of the malnourished child should be explored.

SUMMARY

Six children with kwashiorkor upon admission were found to excrete significantly less 17-hydroxysteroids than five with marasmus although the 17-ketosteroid excretion was not significantly different in the two groups. Eosinophil counts were low in both conditions, but more markedly decreased in marasmus. Intramuscular administration of a single 10 I.U. dose of ACTH produced a sharp rise in the excretion of 17-hydroxysteroids in children with kwashiorkor but had little effect in those with marasmus. With two to eight weeks of treatment these differences disappeared even after stimulation with ACTH.

These findings were duplicated in rats fed a low-protein diet and then given either placebo, cortisone, ACTH or DOCA. Cortisone caused a marked increase in serum albumin and liver protein and a decrease in liver fat but with the other treatments these effects were not noticed. A marked degree of muscle wasting has been demonstrated histologically and chemically in the groups given cortisone. None of the treatments caused any change in the results of the measurements in well nourished rats. Thus, the child with marasmus resembled the protein-deficient rat given cortisone while the child with kwashiorkor was

similar in several basic ways to protein-deficient rats given DOCA or sodium chloride.

By analogy with gluconeogenesis, the term "proteoneogenesis" is used to define the synthesis of liver protein and serum albumin from muscle amino acids. The present findings were interpreted as an indication of predominance of "proteoneogenesis" over gluconeogenesis in the protein-deficient animal in the presence of hyperglucocorticoid activity.

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