Infection and Nutritional Status

II. Effect of Mild Virus Infection Induced by 17-D Yellow Fever Vaccine on Nitrogen Metabolism in Children

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IT HAS recently been emphasized that a variety of infections, including many of viral origin, may act as stress factors to precipitate the development of kwashiorkor in children already suffering from chronic protein malnutrition.[1-3] While many metabolic studies have demonstrated the marked adverse effect of bacterial infections on nitrogen metabolism in man,[4-6] a recent preliminary report of the effect of chicken pox indicates that viral infections also behave in a similar manner.[7]

The preceding paper in this series[8] reports in more detail the effect of chicken pox on the nitrogen intake, absorption, excretion and retention in six boys of preschool age. Four of these children went into negative nitrogen balance during at least one three-day period following the appearance of the exanthem, and the remaining two children showed a marked drop in nitrogen retention.

There is increasing evidence that many viral infections are of so mild and transient a nature as to escape specific diagnosis.[9,10] When dealing with malnourished populations, the possible metabolic effect of even mild viral infections is of considerable practical significance. The present study was planned to determine whether a viral infection as mild as that induced by immunization in young children with the 17-D strain of yellow fever vaccine would cause a detectable effect on nitrogen balance.

MATERIAL

Nine children, who were patients in a private convalescent home for children in Guatemala City, were selected for study at a time when their recovery from various illnesses was well advanced. Their ages and weights are given in Table I.

Children with intercurrent infections were eliminated from the study by careful clinical examination, although one child (V1) was subsequently found to have a giardia infection which was not treated until the study was completed. No temperature elevation above 38.2°c. was observed in any of the children during either before or after vaccination balance periods even though rectal temperature was measured every four hours.

METHODS

The technics for the collection of urine and feces have been previously described.[8] Intervals of one to three days were allowed between periods in two children (V1 and V2); in the remaining children there was no interval between periods. All children were kept on the basal diet for three days before collections were made. On the first day following four three-day balance periods in two children (V1 and V2), and two periods for the remaining children, 0.5 ml. of yellow fever vaccine containing a neurotropic 17-D virus strain was given subcutaneously.‡ This was followed by

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TABLE I
Subjects of Study

Subject	Sex	Age (yr.)	Weight (kg.)
V1	F	8	16.9
V2	M	4	11.7
V3	M	6	18.0
V4	M	8	21.1
V5	M	4	15.1
V7	M	11	21.1
V8	M	4	11.6
V9	M	5	13.4
V10	M	6	12.6

two or four additional three-day balance periods.

The liquid portion of the basal diet was made up of whole milk with added carbohydrate, and the solid part consisted of cooked carrots, bread and bananas. The amounts consumed varied with the child's weight, but the total intake approximated 2.5 gm. of protein and 100 calories/kg. of body weight. All food consumed was weighed and measured and aliquots of the complete diet as well as of the pooled urine and feces for each experimental period were analyzed for nitrogen by the Kjeldahl method. The Student t test was used to evaluate the significance of the differences between mean values.

RESULTS

The average daily intake and the absorption of nitrogen expressed as per cent of total intake are shown in Table II for each individual

TABLE II
Nitrogen Intake and Absorption
After Subcutaneous Injection of the Yellow Fever Virus 17-D Strain
(Three-Day Balance Periods)

Subject	Period					
	I	II	III	IV	V	VI
	Nitrogen Intake (mg. N/kg./day)					
V1	362	473	370*	367†	348	375
V2	524	525	492*	390†	331	384
V3	389	373	386†,‡	405	355§	... ‖
V4	371	350	349†,‡	372	350	...
V5	446	475	464†	436	422	394
V7	473	429	421†	419	407	443
V8	439	451	387†	395	474	429
V9	415§	405	377†	350	452	432
V10	432	422	431†	393	446	406
	Nitrogen Absorption (% of intake)					
V1	66.7	62.7	70.6*	60.0†	61.4	59.5
V2	83.6	91.4	83.8†	83.5†	80.6	75.9
V3	77.0	78.2	79.9†,‡	79.1	76.2§	...
V4	77.0	73.2	65.2†,‡	73.3	59.5	...
V5	82.0	74.6	76.5†	79.4	81.0	83.0
V7	82.1	79.9	81.1†	83.5	81.0	81.4
V8	81.4	80.5	84.9†	81.0	85.3	82.7
V9	78.3§	72.0	84.9†	72.6	77.8	78.9
V10	85.0	79.3	81.3†	73.5	81.2	81.0

* Vaccination against small pox attempted immediately prior to this period with no apparent reaction.
† Yellow fever virus 17-D vaccine injected subcutaneously.
‡ The food nitrogen values were taken from the average of the results of the diet of the other balance periods.
§ Analytical error is suspected but could not be located.
‖ Leaders indicate fecal samples lost.

three day period before and after inoculation with the yellow fever vaccine. Although some of the children occasionally vomited part of a feeding, it was generally possible to maintain the planned intake. The changes in absorption of nitrogen following inoculation with the vaccine were random in direction and not significant.

The retention of nitrogen as per cent of intake and the absolute excretion in the urine are given in Table III. In eight of the nine children, nitrogen retention decreased after inoculation and the decrease was significant at the 5 per cent level. In general, a lowered nitrogen retention was observed in all of the periods after inoculation, whether these extended for six or twelve days. Since intake was relatively constant, the decrease in nitrogen retention was due mainly to an increase in nitrogen excretion in the urine; this is apparent from the nitrogen excretion figures given in Table II. When one nonreacting child (V3) was omitted, the increase in excretion amounted to 7 per cent and was significant at the 5 per cent level. On this basis the retention before inoculation averaged 25.3 per cent and after inoculation 16.7 per cent.

COMMENTS

The 17-D strain of yellow fever vaccine was chosen because it was known to be safe and beneficial, and to produce an immune response in a very high percentage of cases. At the same time it could be expected to produce the effects

TABLE III
Nitrogen Excretion and Retention
After Subcutaneous Injection of the Yellow Fever Virus 17-D Strain
(Three-Day Balance Periods)

Subject	Period					
	I	II	III	IV	V	VI
Nitrogen Excretion (mg. N/kg./day)						
V1	145	142	186*	114†	164	150
V2	334	368	292*	242†	216	235
V3	202	217	218†·‡	229	123§	... ‖
V4	231	216	247†·‡	255	192	...
V5	239	200	259†	241	243	229
V7	209	188	238†	240	213	257
V8	263	262	212†	265	328	292
V9	122§	247	209†	258	310	263
V10	284	240	274†	219	310	300
Nitrogen Retention (% of intake)						
V1	26.7	32.7	20.4*	29.0†	14.1	19.5
V2	19.8	21.0	24.4*	21.5†	15.4	14.7
V3	24.9	20.2	23.5†·‡	22.6	41.6§	...
V4	14.7	11.5	−5.5†·‡	4.6	4.6	...
V5	28.5	32.6	20.8†	24.1	23.4	23.9
V7	38.0	36.0	24.7†	26.2	28.7	23.4
V8	21.6	22.4	30.2†	13.8	16.1	14.6
V9	48.9§	11.0	29.5†	−1.2	9.2	18.0
V10	19.8	22.4	17.8†	17.8	11.6	14.5

* Vaccination against small pox attempted immediately prior to this period with no apparent reaction.
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of a living virus although its virulence has been depressed by repeated transfers in tissue culture.

In view of the mild and afebrile nature of the reaction to this vaccine, it is somewhat surprising that a consistent decrease in urinary nitrogen excretion was detectable. The positive finding supports the contention of various authors, summarized by Peters and Van Slyke[4] and DuBois,[5] that the effect of infection on nitrogen metabolism is due to an actual destruction of protoplasm, rather than an increased metabolic rate due to fever.

The relatively long duration of the effect of even this very mild viral infection is of considerable potential significance. In an earlier study,[11] a single day of mild diarrhea appeared to be associated with one to two weeks of lowered retention, and in subsequent work with chicken pox and mixed bacterial infections,[8] effects were noted for as long as two to four weeks after the acute illness.

In the present study none of the subjects showing a response attained nitrogen retention values equal to those before inoculation within the six to twelve day period of experiment after inoculation. One (V3) of the nine children failed to show any change in nitrogen retention during the first two periods after inoculation, however in the third period, the nitrogen retention almost doubled. Even assuming that the latter represented an experimental error that could not be detected, there is no suggestion of a negative effect of inoculation in this child. It is possible that for some reason the inoculation did not take; perhaps this child had already acquired some degree of immunity.

If only the results in the eight children showing a response are tabulated, the drop in retention averages 30 per cent of the nitrogen intake and 35 per cent of the nitrogen actually absorbed. Among undernourished children a drop of this magnitude in nitrogen retention could well be of practical significance. Since actual diseases of viral origin, even when they are mild, have even greater adverse effects on nitrogen metabolism, they are likely to contribute significantly to the frequency and severity of protein malnutrition among young children in technically underdeveloped areas. It is hoped that these results will encourage further documentation of the effects of viral diseases not only on nitrogen balance but also on the metabolism of other essential nutrients.

SUMMARY

Eight boys and one girl, ranging from four to eleven years of age, and from 11.7 to 21.1 kg. in weight, were inoculated with yellow fever vaccine. Two to four three-day periods in which nitrogen balance was determined preceded and followed the vaccination. The basal diet contained 2.5 gm. of protein and 100 calories/kg. of body weight. Body temperature was measured every four hours throughout all periods and no fever developed in any of the children. In eight of the nine children, nitrogen retention decreased significantly although neither absorption nor intake were significantly affected. It is possible that the inoculation did not take in the child who showed no change in nitrogen metabolism. In the eight children showing a response, the drop in nitrogen retention averaged 30 per cent of the nitrogen intake and 35 per cent of the nitrogen absorbed. The decreased retention was due almost entirely to increased nitrogen excretion in the urine

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