Insulin Secretion in Protein-Calorie Malnutrition

I. Quantitative Abnormalities and Response to Treatment

Dorothy J. Becker, M.B., B.Ch., Bernard L. Pimstone, M.D., M.R.C.P., John D. L. Hansen, M.D., F.R.C.P., D.C.H., and S. Hendricks, Cape Town, South Africa

SUMMARY

Immunoreactive insulin (IRI) responses to oral and/or intravenous (IV) glucose were measured in kwashiorkor and marasmus. Responses were expressed either as peak IRI levels attained or as insulin-glucose ratios. Similar measurements were made in normal controls.

After oral glucose, insulin secretion was abnormally low in every patient with kwashiorkor and in most of the marasmic cases. After IV glucose, normal insulin responses were noted more often, presumably associated with the greater glycemic stimulus. This was particularly noticeable in marasmus.

In both groups of subjects there was improvement after three to six weeks therapy, but this was much more striking after oral glucose. However, in many patients, insulin secretion remained subnormal or even deteriorated at this time, when nutritional status had greatly improved. Two to ten months later however, insulin levels were judged to be within normal limits in these cases. Children known to have suffered from kwashiorkor ten years previously likewise had normal insulin responses in 90 per cent of cases.

Augmented stimulation by glucose plus glucagon revealed some pancreatic insulin reserve in half the untreated patients studied. Yet the responses to augmented testing improved still further in three of five cases after therapy.

Insulin secretion is grossly impaired in kwashiorkor and marasmus. However, it is increased in many cases either by a greater glycemic stimulus or by adding glucagon to the glucose load. This suggests a "sluggishness" of insulin release after glucose under conventional conditions of testing in these cases. The disproportionate improvement after therapy in the insulin response to oral, as opposed to IV, glucose, may provide some evidence that an impaired gut betacytotrophic mechanism is partly responsible for the altered release mechanisms. DIABETES *20*:542-551, August, 1971.

The high protein turnover of the pancreas[1] is thought to make it especially vulnerable to protein depletion. Presumably as a consequence, acinar atrophy[2,3] and impaired exocrine pancreatic function[4] occur in protein-calorie malnutrition (PCM). There is far less clarity concerning the effects of protein depletion on the pancreatic islet cells. Islet cell damage and poor insulin secretion have been suggested to explain the abnormal glucose tolerance of kwashiorkor,[5-7] but studies reported in this context are often incomplete and confusing. Bowie concluded that insulin deficiency seemed unlikely as exogenous insulin failed to increase the glucose disappearance rate.[9] Data based on the bioassay of insulin-like activity (ILA)[10,11] are difficult to interpret because of the nonspecificity of this substance which persists after pancreatectomy.[12,13] Variable levels of fasting immunoreactive insulin (IRI) in PCM[8,14] may simply be a consequence of the known inadequacy of the assessment of insulin secretion by basal measurements only. In studies of insulin responses to glucose stimulation, IRI was reported to have a normal but unsustained peak,[14] and to be decreased[15,16] with improvement after feeding. Deficient insulin responses to arginine[17] and amino acid[15] stimulation in PCM are also recorded. However, the small numbers of patients used in most studies and pooling of individual data have obscured differences in the pattern of insulin secretion in PCM. In some re-

From the M.R.C. Clinical Nutrition Research Unit, Department of Pediatrics and Child Health, and the Isotope Unit, Department of Medicine, University of Cape Town, South Africa.

Requests for reprints should be addressed to Dr. B. L. Pimstone, Department of Medicine, University of Cape Town, South Africa.

ports insulin responses to glucose were only measured days after the introduction of protein into the diet, at a time when they may have already changed. In experimental PCM, Heard has suggested early hyperinsulinism[6,18] and subsequent insulin deficiency.[6,11] To further complicate the issue, insulin antagonism has been noted.[6,11,18]

We report here fifty-four patients with kwashiorkor and marasmus who were studied in an attempt to quantitate individual IRI responses to oral and intravenous glucose. We have also assessed the response to an augmented stimulus of glucose plus glucagon[19] before and after treatment, in order to relate IRI levels to the degree of hyperglycemia and to determine pancreatic reserve.

CASE MATERIAL AND METHODS

I. *Patients studied*

(A) FIFTY-FOUR CHILDREN aged eight to thirty-eight months suffering from PCM were admitted to the metabolic unit of the Red Cross Children's Hospital with either kwashiorkor or marasmic kwashiorkor on the one hand or marasmus with gross growth retardation on the other. Patients with kwashiorkor were underweight with edema and hypoalbuminemia (0.82-2.59 gm./100 ml., mean 1.56 [± 0.07]), and had frequent dermatosis. Marasmic children had weights 60 per cent or less of that expected for their age and had no edema. Their serum albumin levels ranged from 1.61-3.80 gm./100 ml., mean 2.86 (±0.18).

All patients received a protein-free diet with 10 gm./kg. or more carbohydrate in the twenty-four hours prior to testing and were treated with antibiotics, potassium chloride, vitamins and where indicated intravenous therapy. Patients with obvious infection, severe anemia or gross diarrhea were excluded.

(a) *Insulinogenic stimuli given on admission in PCM* (for details see later).

(i) Thirty-nine children were given an intravenous glucose load.

(ii) Twenty-nine children were given oral glucose.

(iii) Fourteen of the above cases received intravenous and oral glucose loads on consecutive days in random order.

(iv) In seven of the fifty-four children, the initial test was followed by an augmented glucose stimulus, in which IV glucagon was given either with intravenous glucose (five cases) or thirty minutes after oral glucose (two cases), depending on the initial test done.

(b) *Tests repeated after three to six weeks feeding*

In all but five children, the initial tests were repeated after three to six weeks of feeding at a stage of apparent clinical and biochemical recovery.

(c) *Tests repeated after two to ten months*

Intravenous or oral glucose loading was repeated in eleven patients whose insulin responses had remained abnormal when retested after three to six weeks of feeding. Tests were performed two to ten months after the initial studies, after careful and continued dietary supervision either at a convalescent home or at the patients' own homes.

(B) A CONTROL GROUP consisted of ten children of similar age group (eighteen to thirty-seven months) whose weight was over the third Boston percentile. All had recovered from unrelated acute infection or were awaiting surgery, and had serum albumin levels significantly above those of our patients (3.42-4.20 gm./100 ml.). However, the levels in two cases were below 3.5 gm./100 ml. which is considered the lowest limit of normal for this population (table 1). An *oral glucose load* was given in five and an *intravenous infusion* in five as defined below.

(C) TEN-YEAR FOLLOW-UP STUDY. (a) Ten children were selected at random from a series at present being followed to assess the long-term effects of PCM. All had been treated for an acute episode of kwashiorkor about ten years previously and had returned to their original environment. Six of this group were below the third Boston percentile for weight. (b) Ten controls in this group were the closest siblings of the above children. They were known not to have suffered acute malnutrition at any time. However, five were below the third Boston percentile for weight. An *intravenous glucose load* (0.5 gm./kg. as a 25 per cent solution) was administered in these twenty cases after an eight to nine-hour overnight fast following a minimum of twenty-four hours of high carbohydrate intake.

Informed consent was obtained from the parents of each child in this study.

II. *Details of test procedures*

All tests were preceded by an eight to nine-hour overnight fast and basal blood sampling for serum albumin, immunoreactive insulin (IRI) and blood sugar.

(a) *Oral glucose load*

Glucose (2 gm./kg. as a 10 per cent solution) was given orally. Serial blood samples were obtained by venipuncture from an external jugular or antecubital vein at thirty-minute intervals for 150 minutes, as timed from the completion of glucose administration.

(b) *Intravenous glucose load*

Intravenous glucose (1 gm./kg. of a 25 per cent dextrose solution) was infused over two minutes and blood

TABLE 1

Serum albumin, IRI peaks, I-G ratios and K values in control subjects

	Age (mths)	Serum albumin (gm./100 ml.)	IRI peak (μU./ml.)	I-G ratio	K
			Oral glucose		
CW	10	3.97	35	3.2	
SA	32	4.20	34	3.8	
PB	13	3.49	31	5.8	
UM	8	3.42	28	4.7	
MW	19	3.91	45	5.6	
Mean	16.4 (±4.32)	3.79 (±0.15)	34.6 (±2.87)	4.62 (±.50)	
			IV glucose		
CB	37	4.19	36	1.2	2.16
JP	12	3.45	72	3.5	2.04
VH	24	4.16	15	0.7	1.54
MS	16	3.72	34	1.3	2.30
TQ	12	3.68	12	0.4	1.93
Mean	20.2 (±4.74)	3.84 (±0.14)	33.8 (±10.71)	1.42 (±0.54)	2.00 (±0.13)

was sampled at 5, 20, 45, 60 and 90 min.

(c) *Augmented glucose stimulus*

Crystalline glucagon, 1 mg. (Lilly, containing 300 microunits of insulin per mg.) was given intravenously, either with the IV glucose or thirty minutes after oral glucose.

III. *Methods*

Serum was immediately separated and frozen until IRI was measured by a modification of the Morgan and Lazarow radioimmunoassay[20] with a sensitivity of 2 microunits/ml. The standard and radioactive tracer was pork insulin (Novo) and the antibody purchased from Wellcome Reagents (Ltd.). All specimens of one individual were run in the same assay, but the variation of the assays from run to run did not exceed 5 per cent.

Blood glucose was estimated by the Somogyi-Nelson technic[21] and serum albumin by the Biuret method.[22]

Insulin-glucose ratios (I-G ratios) were determined by calculating the ratios between the areas under the respective curves (as measured by planimetry) after serial arithmetic plotting of the incremental changes of plasma glucose in mg./100 ml. and IRI in microunits/ml.

The glucose disappearance rate constant (K) after intravenous infusion was calculated as $\frac{0.693}{T½}$ per cent per minute where T½ = the half disappearance time on semilogarithmic plotting of the total blood glucose values.[9,23]

Statistics. Levels of significance were calculated by the Mann-Whitney-U test.

RESULTS

I. *IRI and I-G ratios in controls* (table 1).

The range of insulin responses to oral or intravenous

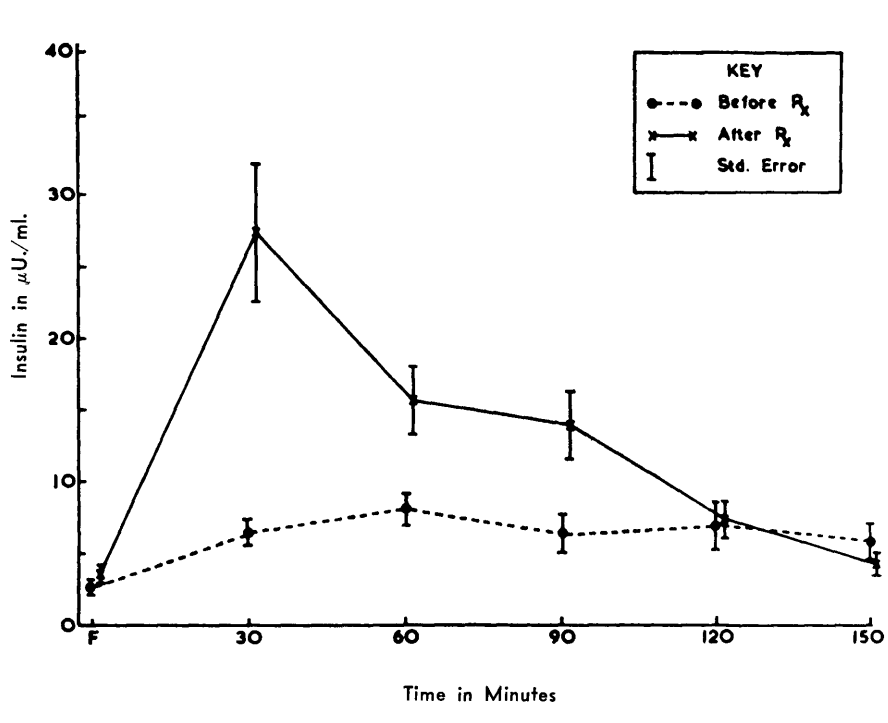

FIG. 1.
IRI responses to oral glucose in twenty-nine cases of kwashiorkor and marasmus. Mean levels are significantly different before and after three to six weeks of therapy thirty minutes ($p < 0.00003$) and sixty minutes ($p < 0.0007$) after the glucose load.

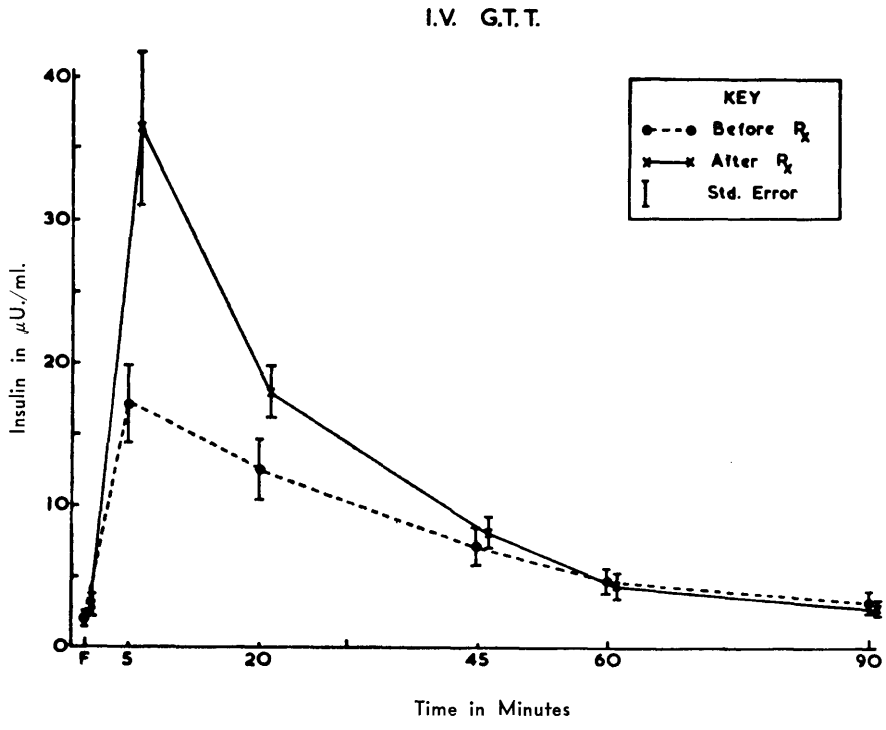

FIG. 2.
IRI responses to IV glucose in thirty-nine cases of kwashiorkor and marasmus. Mean levels are significantly different before and after three to six weeks of therapy five minutes ($p < 0.0007$) and twenty minutes ($p < 0.007$) after the glucose load.

glucose is shown in table 1. Except for two cases in the intravenous group, all peak insulin responses exceeded 20 microunits/ml. Mean peak value after oral glucose was 34.6 (± 2.87) microunits/ml. and after IV glucose, 33.8 (± 10.71) microunits/ml. The two exceptions in the latter group had abnormal K values (less than 2.0)[9,24] and the lowest I-G ratios. These were not however associated with significantly abnormal serum albumin levels. Apart from these two cases all I-G ratios after intravenous glucose were greater than 1.0 and after oral glucose they were all greater than 3.0.

II. *IRI after oral or IV glucose in kwashiorkor and marasmus* (figures 1 and 2).

The IRI responses to *oral glucose* were abnormal in all twenty-nine patients tested. Peaks were less than 20 microunits/ml. except for three cases where responses were unduly delayed and sustained.

After *IV glucose,* twenty-two of thirty-nine peaks were below 20 microunits/ml. The remainder showed higher insulin levels compared to those following oral glucose, associated with the greater increment of blood glucose following the intravenous loading procedure.

After three to six weeks of treatment, the over-all results in *both groups* showed statistically significantly improved insulin responses to the respective stimuli. However, in sixteen of the forty-nine children peaks were below 20 microunits/ml.

III. *I-G ratios in kwashiorkor and marasmus* (figure 3 and table 2).

I-G ratios were significantly lower than controls, whether the glucose load was given orally or intravenously. The abnormalities after intravenous loading were proportionately less than after oral loading and were normal in half the cases of marasmus.

In both groups of subjects, improvement was noted after therapy but was much more striking after oral glucose. In twenty-two of the forty-nine patients I-G ratios remained below 1.0 after IV glucose and below 3.0 after an oral load. Over-all improvement was less significant in marasmus as compared to kwashiorkor. Indeed the mean I-G ratio after IV glucose actually declined after therapy in marasmus.

IV. *Insulin responses after augmented insulin stimulation* (figure 4).

In untreated kwashiorkor, glucagon-augmented glucose stimulation of IRI failed to produce a greater area under the insulin curves than achieved after glucose alone in three of the seven patients tested. This suggests substantial impairment of pancreatic insulin reserve. In the other four patients some increase in the insulin area occurred. After treatment there was a further increment in the response of three of these four cases following augmented stimulation, while the other showed a marked deterioration. One of the patients

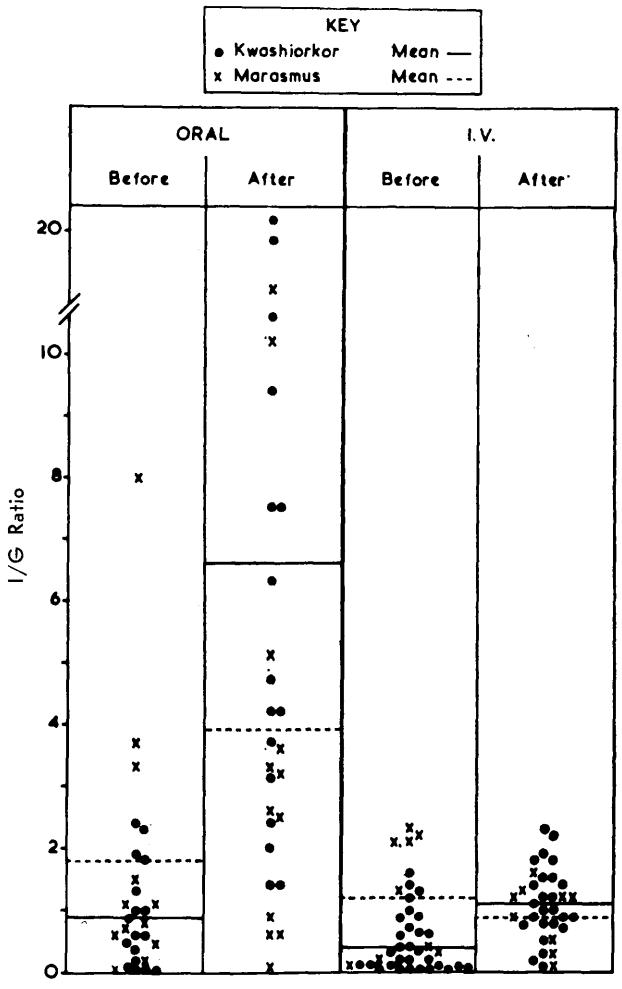

FIG. 3. I-G ratios in kwashiorkor and marasmus after oral and intravenous glucose, before and after three to six weeks of therapy.

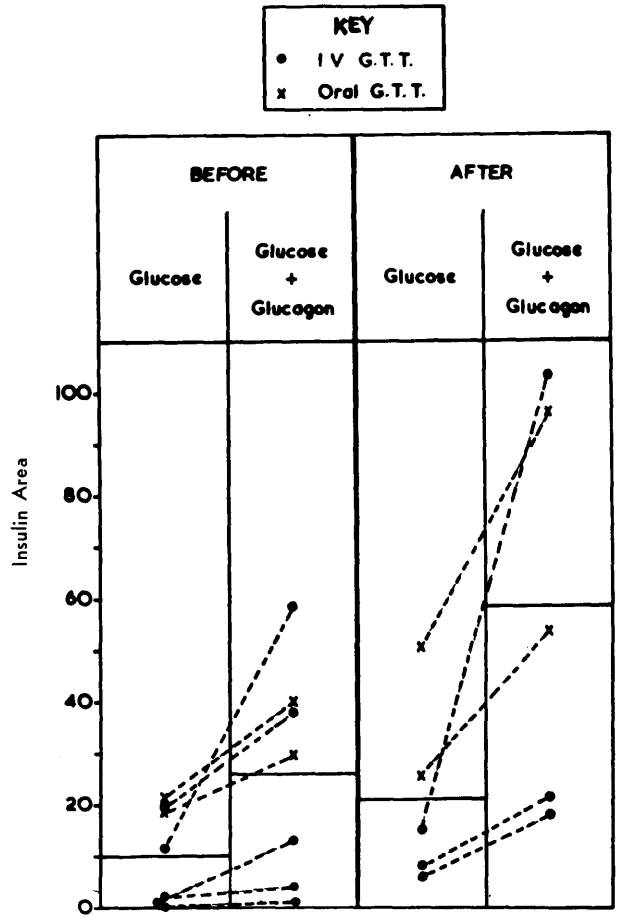

FIG. 4. IRI expressed as areas under the response curves after glucose and glucose plus glucagon stimulation in kwashiorkor before and after three to six weeks of therapy.

with an initially poor response was retested after therapy and was found to have remained unchanged.

V. *Quantitative insulin responses before and after three to six weeks of therapy* (table 3).

Based on I-G ratios, four groups of quantitative responses were defined before and after therapy in kwashiorkor and marasmus. In no instance was there an adequate insulin response to oral glucose in children with untreated kwashiorkor. A striking feature was the large percentage of impaired insulin responses remaining abnormal in both groups, especially in marasmus. In addition, in a few patients the initially normal values actually dropped although often remaining within normal limits. Again this was more noticeable in marasmus.

TABLE 2

I-G ratios in controls and in kwashiorkor and marasmus before and after three to six weeks of therapy

	Oral glucose load		Intravenous glucose load	
	Before	After	Before	After
Controls	4.6 (± 0.50)		1.4 (± 0.54)	
Kwashiorkor	*0.9 (± 0.20)	†6.6 (± 1.40)	§0.4 (± 0.09)	†1.1 (± 0.12)
Marasmus	*1.8 (± 0.65)	‡4.0 (± 1.26)	§1.2 (± 0.33)	0.9 (± 0.17)

*Values in untreated kwashiorkor and marasmus significantly different from controls. Kwashiorkor after oral and IV glucose ($p < 0.001$). Marasmus after oral glucose ($p < 0.01$).
†Values in treated kwashiorkor significantly different from those in untreated patients ($p < 0.0001$).
‡Values in treated marasmus not significantly different from those in untreated patients ($p > 0.05$).
§Values in marasmus significantly higher than those in kwashiorkor ($p < 0.02$).

TABLE 3

Four quantitative patterns of insulin response to glucose (based on I-G ratios) before and after three to six weeks therapy in PCM

Insulin secretion (I-G ratios)		Number of cases			
		Kwashiorkor		Marasmus	
Before therapy	After therapy	Oral glucose	IV glucose	Oral glucose	IV glucose
Normal	Normal	0 (0)*	3 (12)	2 (17)	1 (11)
Impaired	Normal	12 (75)	11 (44)	4 (33)	0 (0)
Impaired	Improved but subnormal	4 (25)	9 (36)	5 (42)	4 (44.5)
Normal	Deteriorated	0 (0)	2 (8)	1 (8)	4 (44.5)
		Total cases			
		16	25	12	9

*The numbers in parentheses are per cent of total cases.

VI. *Quantitative insulin responses after two to ten months of therapy in patients showing persistence of abnormal insulin secretion at three to six weeks* (table 4).

In the eleven cases that were followed eight had improved insulin responses resulting in I-G ratios similar to those of the controls. The other three had peak insulins over 20 microunits/ml. after IV glucose but impaired glucose tolerance resulted in I-G ratios lower than 1.0.

VII. *Insulin secretion ten years after kwashiorkor* (table 5).

Nine of ten recovered cases and nine of ten controls showed peak insulin levels of over 20 microunits/ml. The mean I-G ratio in recovered cases (3.9 [± 0.84]) was not significantly different from that of their controls (3.0 ± 0.44). One case in each group had an I-G ratio lower than 1.0. K values were low in a number of cases without corresponding abnormalities of insulin secretion.

DISCUSSION

Exocrine pancreatic function is extremely vulnerable to protein depletion as evidenced by marked acinar atrophy[2,3] and the low basal enzyme levels and poor responses to stimulation described in children with PCM.[4] The position regarding endocrine function is confused, as decreased granulation and atrophied,[10,25-27] hypertrophied[3,28] and normal islets of Langerhans[29,30] have been variously noted. The limitations of previous studies of ILA and IRI have already been mentioned. Yet the bulk of evidence suggests some deficiency of insulin secretion in PCM.

The interpretation of the quantitative assessment of insulin secretion in environments where malnutrition is common is difficult because of the dearth of suitably matched normal controls of the same racial group. In our study, some age-matched children who appeared to have an overtly normal nutritional status on examination, probably had marginal deficiency states. Our finding of serum albumin levels less than 3.5 gm. per cent

TABLE 4

IRI peaks and I-G ratios in PCM on admission and after three to six weeks and two to ten months feeding

		IRI peak (μU./ml.)						I-G ratio					
		Oral glucose			IV glucose			Oral glucose			IV glucose		
		Before treatment	After 3-6 wks.	After 2-10 mths.	Before treatment	After 3-6 wks.	After 2-10 mths.	Before treatment	After 3-6 wks.	After 2-10 mths.	Before treatment	After 3-6 wks.	After 2-10 mths.
RM	Kwash	8	8	50				0.6	2.4	12.4			
DC	Kwash	13	15	44				0.1	1.4	7.7			
JK	Kwash	1	11	43				0	2.0	7.0			
SG	Kwash				23	10	27				0.7	0.1	0.8
CS	Kwash				18	23	46				0.3	0.8	1.1
BB	Kwash				18	44	53				0.2	0.9	2.0
BM	Kwash				8	21	23				0.1	0.3	0.4
PJ	Kwash				30	11	24				0.4	0.2	0.8
GS	Maras	15	7	13				3.3	0.6	3.2			
CS	Maras	5	4	29	12	38	40	0.5	0.6	3.5	0.2	0.5	1.7
DS	Maras	13	15	18	10	14	37	0.7	2.5	3.1	0.4	0.1	1.5

TABLE 5

Serum albumin and peak IRI, I-G ratios and K values after IV glucose in children ten years after kwashiorkor, and their control siblings

	Age (yrs.)	Wt. percentile	Serum albumin (gm./100 ml.)	IRI peak (μU./ml.)	I-G ratio	K
			Patients ± 10 years after kwashiorkor			
1	12 1/12	3-10th	3.83	62	6.3	1.54
2	11 5/12	3rd	3.91	96	7.3	2.47
3	11 5/12	<3rd	3.54	48	2.3	1.69
4	12	<3rd	3.83	26	1.2	1.93
5	12 6/12	<3rd	4.66	55	2.4	1.82
6	12 4/12	<3rd	4.08	82	2.7	1.80
7	10 9/12	25th	3.53	11	0.3	2.04
8	11 6/12	<3rd	3.74	83	4.4	1.78
9	12 10/12	<3rd	3.31	42	3.5	1.63
10	11 3/12	3rd	3.61	178	8.3	3.30
Mean	11 8/12 (± 0.20)		3.80 (± 0.12)	*68.3 (± 14.76)	*3.87 (± 0.84)	*2.00 (± 0.17)
			Siblings			
1	10 1/12	10th	3.89	58	3.3	1.73
2	13 3/12	<3rd	4.09	75	3.6	2.67
3	12 4/12	3rd	3.94	38	2.0	2.10
4	7	10-25th	3.05	54	2.5	2.07
5	13 1/12	3rd	3.20	52	2.0	1.98
6	14 4/12	<3rd	4.23	58	2.1	1.98
7	12 11/12	<3rd	3.87	54	4.7	1.69
8	12 11/12	<3rd	3.68	78	4.3	2.67
9	11 11/12	<3rd	3.02	96	5.0	3.65
10	8 8/12	3-10th	3.90	15	0.7	1.78
Mean	11 6/12 (± 0.73)		3.69 (± 0.14)	57.8 (± 7.03)	3.0 (± 0.44)	2.23 (± 0.19)

*Values in patients ten years after kwashiorkor not significantly different from those of their controls ($p > 0.05$).

in two of ten controls, low insulin levels in a further two, and abnormal glucose tolerance in four, emphasizes this particular difficulty.

The interpretation of what is normal is also difficult due to the paucity of large surveys of insulin responses to standard stimuli in children, differences in assay methods and standards used, and variations in the manner of expressing results. Grant[31] showed mean peak values of ±25 μU./ml. in a small group of children undergoing diagnostic oral glucose tolerance tests, the range being similar to that reported by Welborn in a large survey in adults.[32] Both authors used an insulin immunoassay method similar to that of the present study. The range of two standard deviations from the mean peak insulin level thirty to sixty minutes after oral glucose in Welborn's study was very large (15-125 μU./ml., mean 44 μU./ml.). Ehrlich[33] reported adult-type insulin responses in five children, while Milinksy[34] suggested that insulin peaks in children after an oral GTT were significantly lower than those of Welborn's adult group. Peak insulin levels after standard oral and IV glucose tolerance tests have been found to be similar.[35] All but two of the control children in this study (table 1) had insulin peaks greater than 20 μU./ml. The two exceptions are considered likely to be abnormal as they are associated with K values below the lower limit of normality for this age group (2.0).[9,24] We have therefore arbitrarily considered an insulin peak of 20 μU./ml. as the probable lowest limit of normal in this study.

The results in our controls were vastly different from those in untreated PCM and similar to recovered cases tested two to ten months later. A group of subjects who had suffered from kwashiorkor ten years before and whose insulin responses to glucose were retested in company with those of previously unaffected siblings, showed higher insulin levels. However, these children were considerably older than our subjects with PCM and cannot strictly be considered controls. The use of patients as their own controls during *short-term* follow-up also proved difficult to interpret as there appeared to be evidence that a number of such children had not attained acceptable levels of insulin secretion after three to six weeks therapy. (Discussed below).

Figures 1 and 2 show quite clearly the low absolute insulin values throughout glucose tolerance tests and the tendency toward improvement after therapy. However,

such an assessment takes no cognizance of the degree of glycemic stimulus. This is particularly relevant in PCM because of the possibility of malabsorption of glucose in some cases[36] and sustained hyperglycemia following glucose. As changes of insulin secretion are only meaningful if the glycemic stimulus is taken into account, insulin-glucose (I-G) ratios were calculated. Such ratios evaluate more closely both the *total* insulin secretion during the course of a glucose tolerance test (not merely the peak height attained) and its relationship to the total hyperglycemic stimulus. There are no reports on I-G ratios in children. After IV glucose loading, the control children in this study had I-G ratios of greater than 1.0 with the two exceptions mentioned above. After oral glucose loading all five control children had I-G ratios of greater than 3.0.

I-G ratios were depressed in kwashiorkor and marasmus after oral glucose. The mean I-G ratio was somewhat but not significantly higher in marasmus (1.8) than kwashiorkor (0.9), in spite of similarly decreased IRI levels in both conditions. However the low IRI peaks in some cases of marasmus were probably a more adequate response to the smaller glycemic stimulus of their more normal glucose tolerance.[9] After intravenous glucose, I-G ratios were low in kwashiorkor, but five of nine marasmic children showed normal I-G ratios, associated in this instance with a greater frequency of normal IRI peaks.

In kwashiorkor, a substantial improvement in I-G ratio after oral glucose loading occurred when the nutritional status improved after three to six weeks of feeding. After IV glucose, by contrast, though I-G ratios were somewhat higher initially, improvement after therapy was less pronounced. In marasmus, the mean I-G ratio following intravenous glucose was not significantly different after this period of therapy. The poor I-G ratios after oral glucose at a time when greater responses frequently followed intravenous infusion, suggests a raised threshold or sluggishness of the insulin releasing mechanism, partly overcome by elevating the glycemic stimulus with IV glucose. Some pancreatic reserve is therefore present. The disproportionate improvement of I-G ratios after oral glucose on treatment may mean that the sluggishness is at least in part, due to a deficiency and later recovery of the gut betacytotrophic factors.[37,38] This will be fully evaluated in a future communication.

Some I-G ratios after oral glucose rose quite remarkably to 10 or more, suggesting the possibility of a transient stage of insulin hypersecretion on recovery in a few cases.

To test pancreatic insulin reserve more efficiently, an enhanced stimulus was given; a number of patients were assessed both after glucose and glucose-glucagon administration. Further insulin reserve was shown by this technic, but it was considerably impaired as compared to the responses following identical stimulation in most of the treated cases.

Table 2 illustrates four different groups of quantitative insulin responses before and after short-term treatment in both kwashiorkor and marasmus. It can be seen that no patient with kwashiorkor showed adequate insulin secretion after oral glucose. In marasmus the apparently normal responses in a few subjects were a result of rapid clearing of their glucose load and consequent normal I-G ratios despite peak insulin levels of less than 20 μU./ml. Most striking are the numbers of patients, particularly those suffering from marasmus, whose insulin secretion was initially normal and deteriorated, or failed to improve after apparently effective therapy. As total calorie depletion plays a more striking role in the marasmic cases, it is conceivable that the insulin required to dispose of their meager carbohydrate and protein intake does not stress even an impaired pancreatic insulin reserve. However, the tremendous increase in protein synthesis and energy requirements during recovery must make substantial demands on insulin production which might not be able to keep pace for a period. More prolonged follow-up (two to ten months) in patients with early persistent abnormalities showed a return to normal of I-G ratios in all but three cases who, however, had normal peak values. This ultimate improvement is borne out by the normal insulin responses in all but one patient tested ten years after kwashiorkor.

A number of tentative conclusions can be drawn from this study. Pancreatic endocrine function is seriously disturbed in protein-calorie malnutrition. Persistently abnormal insulin levels are frequently found on short-term follow-up particularly in marasmus. This has recently been reported by James[15] who concluded that impaired insulin secretion in PCM might be a permanent phenomenon. However, the vast majority of patients with both marasmus and kwashiorkor showed substantial improvement months later, while a group of children known to have suffered acute PCM ten years before, likewise had normal insulin levels. Clearly impairment of insulin secretion is not necessarily permanent after acute PCM and is unlikely to be a major cause of adult diabetes in underprivileged populations of tropical countries.[39,40] Insulin deficiency is probably not incriminated in the genesis of the persistently abnormal glucose tolerance

found years after acute PCM by Cook[41] and in our ten-year follow-up study in which similar K values after IV glucose are noted (table 5). However, our data does not exclude the possible permanent effect on pancreatic endocrine function of more persistent and severe malnutrition during childhood.

Impairment of insulin secretion may not be due to failure of insulin production alone, as a degree of pancreatic insulin reserve is present although clearly impaired. This study does not allow firm conclusions to be drawn regarding the possible mechanisms of the abnormal secretion. However, diminished sensitivity of insulin release is suggested by the rather better insulin peaks and I-G ratios after the larger glycemic stimulus of intravenous as opposed to oral glucose in our untreated cases. The disproportionate improvement after oral glucose when the nutritional status has improved, suggests that an impaired gut betacytotrophic mechanism[37,38] is a contributing factor. Many other possible factors responsible for abnormal insulin secretion remain to be evaluated, for example the role of a low amino acid intake (amino acids have been shown to participate in normal insulin release)[42,43] and the extent of insulin antagonism in selected cases. These will be the subject of communications currently being prepared.

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Influence of Age and Strain on the Response of Rats to Dietary Fructose and Sucrose

(Continued from page 518)

the activity of hepatic glucose-6-phosphatase was assayed.

Rats from five different strains were used: two strains of Hooded rats, a Sprague-Dawley strain, Lister rats, and Wistar rats. The results demonstrated quite a marked strain difference in response to dietary sucrose. Sucrose ingestion significantly depressed fat synthesis from glucose in three groups: the Sprague-Dawley, Wistar, and Lister strains, but not in the two Hooded strains. Three strains (Lister, Wistar, and one Hooded strain) showed a depressed rate of hepatic glucose oxidation and an increased activity of glucose-6-phosphatase. Neither of these parameters was influenced by sucrose ingestion in the remaining two strains.

The authors interpret these observations to support the suggestion that glucose oxidation by liver slices of rats fed sucrose is reduced because of an increase in glucose-6-phosphatase activity. One of the more significant aspects of these results is that they illustrate the fact that the metabolic responses to sucrose ingestion are different in animals having different genetic backgrounds. These studies are consistent with earlier reports showing strain differences in response to dietary sucrose (M. W. Marshall and H. E. Hildebrand, J. Nutr. *79*:227, 1963; A. M. Durand, M. Fisher, and M. Adams, Arch. Path. *85*:318, 1968).

These two reports taken together are of considerable importance in illustrating some areas in which caution should be observed in animal and human experimentation related to the metabolic effects of dietary carbohydrates, particularly sucrose and fructose. It is well recognized that individual differences exist in the human population with regard to carbohydrate metabolism. The many abnormalities of carbohydrate metabolism which have been reported illustrate this point (Nutr. Rev. *28*:153 and 204, 1970). However in dealing with laboratory rats we often assume that all are similar.

The report of Bender et al. reminds us that this is not necessarily the case, and that this needs to be considered in extrapolating results from one strain of rat to another; and extrapolation from one species to another should be attempted only with extreme caution. The report of Hill demonstrates that the age of animals is also an important factor to consider in studying metabolic responses to dietary carbohydrate. This observation may well explain some of the apparent inconsistencies found in the literature. The significance of age with regard to the lipogenic effects of various dietary carbohydrates in human beings remains to be studied. In view of the current discussions as to the possible role of dietary sucrose in the development of cardiovascular disease, this is a point that needs to be resolved.

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