METABOLISM STUDIES IN CÆLIAC DISEASE

BY

OLIVE MACRAE, M.D., and NOAH MORRIS, M.D., B.Sc.

(From the Department of Pædiatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

Since the publication of Cheadle's paper¹ in 1903, the presence of excess of fat in the fæces has attracted much notice as the most characteristic sign of the metabolic disturbance in cœliac disease. It has been recognized that associated with this disturbance of fat absorption, there occurs also a defective retention of minerals and an excessive loss of nitrogen in the fæces. In consequence some attention has been paid to the effect of varying the composition of the dietary, especially from the therapeutic standpoint. The inter-relationship of the disturbances in the absorption of the various elements of the diet is a matter of importance both from the practical point of view, and because of the possible value in the explanation of other metabolic disorders. Parsons² has already indicated the importance of vitamin D in the prevention of cœliac rickets, showing that the continued absence of this vitamin from the fat-poor diets used in treatment is the cause of the rickets of convalescence. The series of observations detailed in this paper are published in the hope that some further light may be thrown on the underlying chemical pathology of the cœliac state. A more complete understanding of the disorder should ultimately prove of value in the prevention and cure of the disease.

Metabolic studies in cœliac disease are subject to the great disadvantage that sudden changes occur in the condition of the patient although the diet is constant and the environment unaltered. Accordingly it is difficult to determine whether differences in the metabolic findings are to be attributed to changes in food or other treatment, or to natural aggravation or amelioration of the condition. In these investigations as much care as possible was taken to rule out the idiopathic changes in the severity of the disease. A brief description of the salient features of the case-histories of the patients is appended at the end of the paper (see Appendix). It is proposed in the first place to summarize the metabolic findings with regard to the various forms of foodstuffs and thereafter to discuss the bearing of these results on the chemical pathogenesis of cœliac disease.

Utilization of fat (see Table 1).—A characteristic feature of cœliac disease is the presence of a large amount of fat in the fæces which are bulkier than normal. Frequently they are whitish and fatty in appearance, but this depends to a large extent on the intake of fat. It has been stated that there may take place a re-excretion of fat through the intestinal epithelium and

TABLE 1.

SHOWING PERCENTAGE AND ABSOLUTE DAILY CONTENT OF FÆCAL FAT WITH PERCENTAGE AND ACTUAL DAILY UTILIZATION.

Case No.	Days	Diet*	Dried faeces gram.	% fat in dried faeces	% of faecal fat			Daily output				Utilization			
					N.F.	F.F.A.	C.F.A.	N.F.	F.F.A.	C.F.A.	Total fat gram.	Intake gram.	Absorption		
													Total gram.	%	per kgrm. body wt.
1 (i)	6	N	11.49	32.70	11.6	28.8	59.2	0.43	1.09	2.23	3.77	29.4	25.61	87.2	3.5
(ii)	6	H	11.99	50.00	13.4	24.8	61.6	0.80	1.48	3.68	5.98	99.2	93.22	94.2	12.1
(iii)	7	N	15.70	50.94	20.9	40.4	38.6	1.67	3.22	3.09	7.99	24.2	16.21	67.0	2.2
(iv)	7	H	32.20	57.51	17.0	35.1	47.7	3.17	6.49	8.87	18.53	97.0	78.47	80.9	10.7
(v)	7	H(a)	16.81	55.74	11.1	31.4	57.4	1.04	2.96	5.40	9.40	97.0	87.6	88.8	10.4
(vi)	6	N	6.62	44.50	5.6	69.9	24.4	0.15	2.07	0.72	2.94	24.0	21.1	87.6	2.4
(vii)	6	H	14.79	81.20	2.5	41.6	55.7	0.31	5.05	6.75	12.11	104.3	92.2	88.4	10.6
(viii)	5	H(b)	11.50	70.20	11.4	35.5	52.4	0.97	2.90	4.27	8.14	104.3	96.2	92.2	10.1
2 (i)	6	N	12.55	35.60	22.3	54.1	24.0	0.99	2.38	1.08	4.45	34.1	29.6	87.2	3.4
(ii)	6	H	11.95	38.35	18.2	47.5	36.6	0.83	2.17	1.56	4.56	99.9	95.3	95.4	10.8
(iii)	7	N	7.99	47.60	11.9	39.0	50.0	0.45	1.46	1.90	3.81	27.1	23.8	86.0	2.8
(iv)	7	N	12.42	48.00	18.1	65.8	16.0	1.09	3.92	0.96	5.97	35.0	29.0	83.1	3.3
(v)	7	N	20.10	53.00	13.3	51.4	35.3	1.41	6.91	3.76	12.08	38.4	26.4	68.7	2.5
(vi)	7	H	17.03	66.80	15.2	41.7	43.1	1.74	4.73	4.90	11.37	75.1	63.7	84.8	6.0
(vii)	7	H(b)	18.57	64.98	18.2	46.0	35.6	2.20	5.57	4.30	12.07	75.1	63.0	83.9	5.6
3 (i)	6	N	18.45	40.45	20.9	48.8	30.2	1.58	3.63	2.25	7.46	28.2	20.7	73.6	2.5
(ii)	6	H	29.77	74.58	20.5	48.6	30.9	3.93	9.37	8.90	22.20	114.7	92.7	80.8	11.6
(iii)	6	H	39.73	73.95	22.5	53.1	24.4	6.60	15.58	7.17	29.35	126.8	96.4	76.0	12.1
(iv)	6	H(a)	33.25	69.40	21.6	45.4	32.9	5.00	10.50	7.60	23.10	126.8	103.7	81.8	12.3
(v)	7	L	19.33	25.98	17.0	49.9	32.6	0.87	2.50	1.64	5.01	8.1	3.1	38.2	0.3
(vi)	7	N	23.13	49.10	7.2	26.8	65.8	0.83	3.05	7.48	11.36	25.5	14.1	55.3	1.5
4 (i)	6	N	8.23	26.82	20.3	37.3	42.6	0.45	0.82	0.93	2.21	26.6	24.4	91.0	4.1
(ii)	7	N	16.73	39.02	15.7	50.3	34.0	1.03	3.30	2.21	6.54	20.5	14.0	68.1	2.1
(iii)	7	N(c)	13.57	49.01	5.1	19.9	74.9	0.34	1.32	4.99	6.65	17.9	11.3	62.8	2.0
5 (i)	7	N	28.31	35.03	13.2	72.4	14.4	1.32	7.17	1.42	9.91	34.6	24.7	71.3	3.7
(ii)	7	N	37.17	44.55	39.4	40.9	19.6	6.50	6.86	3.25	16.61	21.0	4.4	20.9	0.8
6 (i)	7	N	16.90	58.70	13.6	48.3	38.3	1.33	4.78	3.80	9.91	38.8	28.9	74.4	2.6
(ii)	6	H	13.14	62.75	13.8	26.5	59.8	1.32	2.55	5.75	9.62	115.0	105.4	91.6	9.4

*L. Low fat intake.

N. Normal fat intake.

H. High fat intake.

(a) NaH_2PO_4 added.

(b) Sodium glycocholate added.

(c) Radiostol added.

Fanconi³ gives figures showing an excretion of 28.55 gm. of fat although the intake only amounted to 20.66 gm., thus indicating a re-excretion of almost 8 gm. of fat in the twenty-four hours. Schick and Wagner⁴ found a greatly increased percentage of neutral fat, but it is generally agreed the fat-splitting is quite normal. Fanconi describes two types as regards the disturbance in fat absorption, first a group in which the absorption is very poor and where most of the fat is unsplit, and secondly a group in which, despite poor absorption, the splitting is normal.

In our series the neutral fat formed less than one-quarter of the total faecal fat except in one period in one Case 5 (ii), when the child was obviously going down-hill rapidly. In that period 39.4 per cent. of the total fat was unsplit which could not have been accounted for by increased peristalsis as the daily number of motions was only one or at most two. Otherwise the results of the faecal analyses indicated excellent fat splitting in most of the cases, and that although the percentage absorption was below normal.

FIG. 1. Showing percentage absorption of fat during different daily intake of fat in health and coeliac disease.

The percentage absorption of fat varied in the individual cases and at different times. Generally it bore a rough relationship to the clinical condition of the patient, provided one kept in mind the actual amount of fat ingested. Harrison and Sheldon⁵ state that the finding of a high percentage of total fat in the faeces does not necessarily indicate coeliac disease, but that a normal result in an untreated patient is almost definitely against the diagnosis of coeliac disease. In Case 1 (ii), however, the fat formed half the weight of the dried faeces, whereas in Case 5 (i) only a third, i.e., within normal limits, although the former patient was convalescing rapidly and steadily and the latter was in an acute stage. The percentage absorption was in Case 1 (ii) 94.2 per cent. and in Case 5 (i) 71.3 per cent. It is therefore impossible to

judge of the absorption of fat from a knowledge alone of the percentage composition of the faeces. It is essential to have figures for the fat intake and the weight of the dried faeces so that the percentage absorption of the intake can be calculated.

It has been shown by Hutchison⁶ and others that in health the fat forms about one-third of the weight of the dried faeces. Accordingly an increase in the intake of fat will lead to both an absolute and relative increase in its absorption provided the faeces are not excessive in amount. The results charted on Fig. 1 indicate the percentage absorption of fat with varying daily intakes in a series of children, either healthy, or at any rate without gastro-intestinal disorder. If one takes into consideration the varying norm in different individuals the gradual rise in the curve as the intake of fat is increased is all the more striking. When the percentage absorption of fat on varying intakes is estimated in the same individual it is invariably found to increase with the rise in the absolute amount of fat ingested. This held good with a daily intake of some 290 grm. of fat. It is therefore justifiable to conclude that in health the absorptive power of the intestine for fat is practically unlimited, provided, of course that the excess of fat does not lead to intestinal upset.

When the results of the coeliac analyses are examined it is clear that here too the percentage absorption of fat rises with the increase in the daily intake. This can obviously only hold good in the one individual at any particular phase of the coeliac condition owing to the different grades of severity of the disease in different patients and in the same patient at different times. It might be suggested that the lower percentage absorption on the lower fat diet was due to an aggravation of the coeliac state. In all cases, however, the high fat diet followed immediately on the moderate, and everyone is agreed that high fat diet is not beneficial to the coeliac patient. One point of difference between the behaviour of the normal and the coeliac to the increased ingestion of fat is the much greater increase in the weight of the dried faeces in the coeliac patient. Despite this increase in faecal weight, both the absolute and percentage amounts of fat absorbed were greatly raised. The percentage of total fat in the dried faeces was invariably raised as a result of a higher fat intake. The ratio of neutral to total faecal fat remained practically unchanged, tending if anything, to be rather lower on the high fat diet. The combined fatty acids (calcium soaps) became appreciably greater in amount both absolutely and relatively to faecal weight and total fat.

EFFECT OF ACID-SODIUM PHOSPHATE.—Administration of di-hydrogen sodium phosphate during a high fat period caused a definite increase in the ratio of insoluble soaps to total faecal fat and faecal weight. The percentage absorption was increased quite markedly in both cases. It would seem therefore that this substance promotes conditions favouring fat absorption.

EFFECT OF SODIUM GLYCOCHOLATE.—The effect was to increase the relative and actual amounts of neutral fat with corresponding diminution in those of the insoluble soaps. The percentage absorption of fat showed a marked increase in one and a slight reduction in the other case. It would appear that glycocholate promotes the absorption of the soaps.

EFFECT OF RADIOSTOL.—The percentage absorption of fat was slightly diminished. The absolute amount of combined fatty acids in the faeces was greatly increased as was the ratio of combined fatty acids to total fat. A similar effect of vitamin D preparations has been noted in metabolism studies on rickets (MacRae?).

The ability of the coeliac patient to deal with fat in the intestine is undoubtedly impaired. During the active stage the percentage absorption is below normal while as a general rule the fat-splitting properties of the intestinal juices are quite up to standard. The defect in fat absorption is much more marked when the intake is low. During a period of high-fat intake the percentage absorption rises usually to a very marked degree. Accordingly the actual amount of fat absorbed during such a period usually exceeds the normal requirements of the child although the percentage absorption is still below the normal figure for that particular daily intake of fat.

It is generally held that administration of fat in large amount immediately produces a recurrence of active symptoms. By this is meant the re-appearance of bulky fatty motions. Two patients, Cases 1 and 2, were given high fat diets for a period of 14 days during a quiescent stage when the fat absorption was about 90 per cent. The fat absorption on the increased fat intake became greater both relatively and absolutely, being quite within normal limits. The motions were practically unchanged in weight and did not present any abnormal appearance. Shortly after this high fat period the patients were discharged without symptoms on a low-fat high-protein diet and remained well for several months only to return with a recurrence of the manifestations of the active disease. It seems justifiable to conclude from this experience that administration of large amounts of fat in a stage of true convalescence does not, for short periods at any rate, lead to recrudescence of symptoms. If, however, the patient is only apparently convalescent, the addition of fat to the diet will lead to the appearance of typical coeliac motions. It is questionable how far the appearance of these fatty stools is indicative of an aggravation of the condition. Even if the percentage absorption of fat were much below normal, fatty stools could not occur when the fat intake was low. Accordingly when such a patient, who has been receiving a minimal amount of fat, ingests more fat, there will appear in the faeces a much greater amount of fatty products than normal, leading to the formation of typical coeliac motions. This gives rise to the impression that the condition has been aggravated although the presence of fatty motions is merely an indication that the intestine is at the time unable to deal properly with fat. Naturally this was not evident on the minimal fat diet as the amount of fat in the food was insufficient to give bulk to the faeces, although the intestinal condition was no better than during the period when the stools were large and fatty.

The varying effects of the administration of acid phosphate, high-fat diet, vitamin D, and sodium glycocholate on the distribution of fat in the faeces are of interest. The first three lead to an increased amount, relatively at any rate, of calcium soaps, whereas glycocholate produces a decrease in the soaps and

presumably an increased absorption of fat in that form. Verzàr and Kúthy⁸ maintain that absorption of fats as soaps is impossible unless at a pH of 9 when the soaps are soluble. One of the main functions of the bile salts is to make the soaps soluble at an acid pH which is the normal for the intestine. Klinke⁹ also states that calcium soaps are soluble in the presence of bile salts. Adler²⁷ showed that withdrawal of the bile secretion led to an appearance of calcium soaps which greatly diminished in amount on administration of bile-salts. Our results show that increasing the acidity of the gut by the presence of excess fatty acids, or administration of acid salt or by ingestion of vitamin D raises the proportion of fat found as insoluble soaps. It would therefore seem justifiable to conclude that in these cases the reaction of the intestine is alkaline. The question remains how far this reaction is due simply to the associated vitamin D deficiency which has become secondarily superimposed on the coeliac condition. Sodium glycocholate decreases the absolute and relative amounts of the insoluble soaps. Accordingly it would appear that there is a deficiency in bile salt or at any rate that addition of bile salt is an aid to the absorption of soaps in the coeliac state.

Lime and phosphorus (see Table 2).—The daily retention of lime and phosphorus on a moderate fat-diet, when calculated on the basis of kilogramme of actual weight is either normal or slightly subnormal. The total amount retained, however, is much below that found in the healthy child of the corresponding age, owing to the dwarfism and greatly reduced weight of the coeliac child. Linder and Harris¹⁰ state that the calcium utilization has a rough relationship to the total fat output, being high only when the fat excretion is low. Generally this may be so, but there are numerous exceptions, and it would be unwise to deduce a low calcium retention because of high fat content of the fæces. Thus in Case 2 (vi) there was an average daily excretion of 11.4 grm. fat while the calcium retention was quite good (47 mgrm./kgrm./day), whereas in the previous period when the fat output was practically the same (12.1 grm./days) there was a marked negative retention.

Further evidence that the bulk of faecal fat cannot be taken as the cause of low calcium retention is obtained from a consideration of the mode of mineral excretion in jaundice. In this condition there is a faulty absorption of fats, the splitting of which is quite normal. The mineral retention is low but while the bulk of the calcium is found in the fæces by far the greater part of the phosphorus is excreted in the urine. The $\text{CaO} : \text{P}_2\text{O}_5$ ratio of the fæces and the urinary P_2O_5 : faecal P_2O_5 ratio are both abnormally high. This is attributed to the large amount of fatty acid fixing the calcium in the intestine and so liberating much phosphorus to be absorbed and subsequently excreted in the urine.

The results in coeliac disease bear a strong resemblance as far as the mode of mineral excretion is concerned to those seen in rickets where the bulk of the phosphorus is found in the fæces. In rickets, the fat content of the fæces is not raised; indeed it is during healing that the amount of soaps is relatively and absolutely increased.

EFFECT OF HIGH FAT DIET.—In two experiments this produced a very marked increase in the amount of faecal calcium. In the third, the faecal calcium was quite markedly diminished with a consequent rise of the retention of lime. An increased amount of phosphorus was found in the urine in all three cases. This increase in urinary phosphorus cannot be taken as evidence of increased absorption of phosphorus since in the first two experiments (Case 1, iv and vii) the amount found in the faeces was also increased. Only in the third (Case 2, vi), which showed a decrease in faecal calcium was the phosphorus

TABLE 2.

(CALCIUM AND PHOSPHORUS METABOLISM: DAILY INTAKE, OUTPUT AND RETENTION.)

Case No.	Days	Diet*	CaO (gram.)				P ₂ O ₅ (gram.)				Urine P ₂ O ₅ × 100	Faecal P ₂ O ₅ × 100	Faecal CaO × 100	Faecal P ₂ O ₅ × 100	Retention gram. per kgm.	
			Intake	Faecal output	Faecal output as soaps	Urinary output	Total reten- tion	Intake	Faecal output	Urinary output	Total reten- tion				CaO	P ₂ O ₅
1	(iii)	7	N	1.223	1.043	.31	.053	.165	1.791	.972	.421	.399	43.2	103	-.022	-.055
	(iv)	7	H	.973	1.577	.887	.065	-.669	1.495	.998	.562	-.064	56.3	158	-.093	-.009
	(v)	7	H(a)	.976	.823	.54	.126	.026	3.007	.756	.967	1.284	128.0	109	-.004	-.178
	(vi)	6	N	1.21	.734	.072	.023	.457	1.81	.913	.361	.542	40.0	80.4	-.051	-.061
	(vii)	6	H	1.15	1.14	.67	.025	-.008	1.79	1.005	.63	.159	62.6	113	-.001	-.018
	(viii)	5	H(b)	1.205	.747	.426	.025	.432	1.835	.540	.676	.618	125	138	-.045	-.066
	(v)	7	N	1.80	2.31	.375	.037	-.548	2.64	2.090	.368	.181	18	110	-.053	-.017
	(vi)	7	H	1.825	1.311	.490	.021	.493	2.25	1.158	1.031	.061	8.9	113	-.047	-.006
	(vii)	7	H(b)	1.775	1.69	.43	.026	-.059	2.287	1.43	1.042	-.185	72.8	118	-.005	-.016
4	(i)	6	N	1.287	.650	.093	.031	.606	1.618	.535	.363	.721	68	121	-.10	-.118
	(ii)	7	N	1.48	1.372	.221	.020	.087	2.406	1.606	.311	.489	19	85	-.013	-.075
	(iii)	7	N(c)	1.497	1.085	.499	.026	.385	2.391	.597	1.204	.589	202	181	-.060	-.094
6	(i)	7	N	1.987	1.673	.378	.022	.292	2.687	1.538	.624	.525	40.6	109	-.028	-.050
	(ii)	6	H	1.890	1.211	.575	.013	.649	2.849	.904	1.10	.845	121	66	-.053	-.069

*L. Low fat intake.

(a) NaH₂PO₄ added.

N. Normal fat intake.

(b) Sodium glycocholate added.

H. High fat intake.

(c) Radiostol added.

in the faeces diminished. In all three instances the total amount of faecal fat was increased as was that of insoluble soaps. Accordingly since the increased retention of lime and phosphorus occurring in Case 2 (vi) took place simultaneously with an increase in faecal fat and soaps, it seems justifiable to argue that the amount of fat in the faeces cannot be more than a secondary factor in hindering the absorption of minerals.

Further, although in Case 1 (iv) and (vii), we find that about 4 gram. extra CaO was fixed as soaps there was no apparent liberation of phosphorus, since

that element was actually increased in amount in the fæces. This is in contrast to the picture met with in jaundice where there is an increased fæcal amount of calcium soaps associated with a diminished fæcal content of phosphorus and an increased excretion of phosphorus in the urine. As already pointed out the increase in urinary phosphorus in these cases has been attributed to an increased intestinal absorption of phosphorus liberated as a result of the increased fixation of calcium as soaps. In cases of cœliac disease on the other hand, there is no evidence of increased absorption of phosphorus as with the increased formation of calcium soaps there is also an increased fæcal phosphorus. It seems fair to conclude, therefore, that the extra urinary phosphorus was not the result of increased absorption.

As regards Case 2 (vi) it might be argued that the increased mineral retention took place during a period of general improvement. That this was not so is indicated by the low percentage absorption of fat for the amount ingested. We have evidence that during this period the carbohydrate metabolism also showed signs of definite impairment. Accordingly it must be admitted that during this period there occurred a marked improvement in the retention of lime and phosphorus, although all the other metabolic findings showed no signs of betterment.

There remains one hypothesis, namely, that the poor retention of minerals is the result of deficiency in vitamin D. Parsons² states that the development of rickets in cœliac infantilism is due primarily to the deficient absorption of fat and therefore of vitamin D, calcium and phosphorus. The 'rachitic' mode of mineral excretion is in this connection very suggestive. Further, in agreement with Parsons and other workers, we have found the values for serum calcium and inorganic phosphorus to be low (Table 6). We have studied the effect of vitamin D administration in one case and find that there is a very marked increase of lime and phosphorus retention, and that the main excretory route of phosphorus is shifted from fæces to urine. Further, the percentage absorption of fat is slightly reduced and the weight of fæcal fat is increased, thus affording still more proof that the metabolism of fat and of minerals in cœliac disease are only secondarily connected. The increased retention of lime during the high-fat period in Case 2 (vi) would on this line of reasoning be explained by the increased absorption of vitamin D resulting from the increased intake of fat. The change in the distribution of calcium between phosphorus and soaps and the divergence of the phosphorus from fæces to urine during the high fat period bear a close resemblance to the observations in healing rickets.

In the other two periods, Case 1 (v) and (viii) with high fat the changes in distribution of lime and phosphoric acid, as indicated by the ratios fæcal CaO to fæcal P_2O_5 and urinary P_2O_5 to fæcal P_2O_5 , are very similar to those seen in Case 2. The retention of these minerals was, however, greatly reduced, and this despite the fact that a much larger actual amount of fat was absorbed by the patient in these two periods than in the case of Case 2 (vi). Linder and Harris¹⁰ put forward the suggestion that most of the sterols remain with the unabsorbed fat in the gut. Even if this is correct, it would not explain

the marked difference in the results since it would be expected that the greater amount of fat absorbed would carry with it a larger moiety of the sterols. It seems to us that the explanation lies in the larger amount of fat absorbed by Case 1 leading to the production of a ketosis the effects of which overshadow the influence of increased vitamin D absorption. We have shown¹¹ that the osseous tissues play an important part in getting rid of excess of acid substances, and as a consequence during the administration of an acid-producing substance such as ammonium chloride there occurs a great increase in the excretion of calcium both by the urine and faeces. A similar occurrence takes place in conditions of ketosis. Of the presence of ketosis during the high-fat periods of W.B., further proof is given by the rise in excretion of the titratable acid and ammonia in the urine. In addition, the renal excretion of lime is slightly increased during these periods although the retention is diminished. Admittedly the increase in urinary output is very slight but it must be remembered that the store of lime is much below normal as is indicated by the radiographic evidence of marked osteoporosis. In the high-fat period in Case 2, on the other hand, where a great retention of lime took place the urinary output of this substance was slightly diminished.

If this line of reasoning be correct then it would appear that the low retention of minerals during the high-fat periods of Case 1 must be attributed to the effect of ketosis more than neutralizing the influence of the extra vitamin D made available by the increased absorption of fat. This naturally involves the assumption of a re-excretion of lime by the gut. This view however, is supported by the strong experimental evidence of Percival and Stewart²⁸ and other workers. Indeed in two of the series recorded here there was much more calcium excreted in the faeces than was ingested:—0.51 gm. in Case 2 (v) and 0.60 gm. in Case 1 (iv).

EFFECT OF NaH_2PO_4 .—The effect of NaH_2PO_4 was to decrease the amounts of faecal calcium and phosphorus although there was a greatly increased ingestion of the latter substance. This must be due either to an increased absorption or diminished re-excretion into the gut. Simultaneously there was a decrease in the amount of faecal fat although the relative amount of soaps was increased from 47.7 to 57.4 per cent. of the total faecal fat. The ketogenic action of the increased fat absorption must have been present: therefore it seems safe to assume that the mineral excretion must have played as great a part as in the previous period in combating the acidosis. It would therefore appear that the action of the NaH_2PO_4 was to increase the absorption of lime and phosphorus, so that the increased output resulting from ketosis was rather more than neutralized by the increased absorption. It is impossible to decide whether calcium or phosphorus was primarily affected. It seems reasonable, however, to suggest that the excess of phosphorus in the gut attracted some of the calcium from the fat, and that the combination of phosphorus and calcium was rendered more easily absorbed by the presence of an acid reaction in the gut due to the presence of excess fatty acids and acid sodium phosphate.

EFFECT OF SODIUM GLYCOCHOLATE.—In one case there was a marked increase in the retention of lime and phosphorus while in the other there was a definite decrease. On the whole this was in conformity with the effect on the absorption of fat since in the second there was an increase in the amount of faecal fat. With the data at our disposal it is not possible to explain this variability in the action of sodium glycocholate.

CONCLUSIONS.—On summing up the findings on mineral metabolism the following conclusions seem justified :—

1. The retention of lime and phosphorus is low while the patient is on a normal diet. The loss of these elements is mainly by the gut. While the retention of calcium is, generally, inversely proportional to the amount of faecal fat, this is not invariable as an increased retention may occur in spite of a rise in the amount of fat in the motions. The retention of calcium can therefore only be secondarily related to the utilization of fat.

2. Administration of vitamin D raises the retention of lime although the absorption of fat is certainly not increased.

3. Increase in the absorption of fat leads to an increased absorption of lime. If the increased absorption produces a ketogenic effect, the rise in the amount of lime absorbed is masked by an increased re-excretion. The increased absorption of lime is probably the result of an increase in the absorption of vitamin D and an increase in the acidity of the intestinal contents.

4. The effect of rendering the intestinal contents more acid is exemplified by the increased absorption of lime during administration of an acid salt (NaH_2PO_4).

From these findings it would appear that the poor calcium absorption in coeliac disease is due to a lack of vitamin D and inadequate acidity of the intestinal juices. Any factor which leads to an increased utilization of fat containing vitamin D without undue ketogenic effect will produce a rise in vitamin D absorption and consequently an increase in calcium retention as in the sodium glycocholate period of Case 1.

Utilization of carbohydrate (see Tables 3 and 4).—It is a well recognized clinical fact that patients with coeliac disease do not tolerate carbohydrate well. Starchy foods undergo fermentation, and as indicated by the frequent presence of starch granules in the faeces are not well digested. This might, of course, be due to the large bulk of the intestinal contents, which prevents the amylases reaching the starch as quickly as usual, and so allowing fermentation to take place.

The ability of the intestine to absorb simple monosaccharides is very difficult to test. Schaap¹² found values of faecal carbohydrate higher in coeliac disease than in any other condition. McCrudden¹³ on the other hand states that the lower fatty acids which are formed from carbohydrates are if anything less in coeliac stools than normal. Poynton and Cole¹⁴ have reported one case of coeliac disease showing glycosuria: this might have been due to low renal threshold independent of the coeliac condition or possibly was the result of previous carbohydrate starvation. The frequent existence of acetonuria is undoubtedly the result of defective supply of carbohydrate in the diet.

TABLE 3.
BLOOD-SUGAR CURVE IN CELIAC DISEASE

Case No.	Wt. in kgrm.	Blood-sugar (mgrm. per 100 c.cm.) after glucose (1 grm. per kgrm. body wt.)					Remarks
		Fast-ing	30 min.	60 min.	90 min.	120 min.	
1	8.60	77	83	87	79	81	Typical celiac motions.
	8.60	79	67	73	75	67	„ „ „
	8.60	100	85	79	85	85	„ „ „
2	9.40	77	73	83	77	84	„ „ „
	9.40	95	79	77	73	67	„ „ „
	10.17	58	66	85	66	60	„ „ „
	10.63	67	67	67	67	—	„ „ „
	10.30	104	100	104	100	—	„ „ „
	11.25	63	104	100	122	113	After 14 days' of sod. glycocholate
5	6.54	81	72	72	81	—	Absorp. of fat = 71.3%
6	10.33	106	104	102	98	112	„ „ „ = 74.4%
	11.62	82	89	136	109	97	„ „ „ = 91.0%
4	5.54	85	106	104	102	100	„ „ „ = 91.0%
	5.80	83	87	106	102	100	„ „ „ = 68.1%
7	15.5	89	109	109	109	100	Large fatty motions.
	17.0	115	139	170	147	98	Motions apparently quite normal.

TABLE 4.
BLOOD-SUGAR CURVE IN NON-CELIAC STEATORRHEA.

Name	Age	Wt. in kgrm.	Blood-sugar (mgrm. per 100 c.cm.) after glucose (1 grm. per kgrm. body wt.)					Condition of patient
			Fast-ing	30 min.	60 min.	90 min.	120 min.	
J.T.	10 yr.	17.90	82	134	206	159	109	Chronic intestinal indigestion.
I.W.	1½ „	9.80	94	94	122	152	139	Chronic intestinal indigestion.
A.O'B.	7 „	22.45	104	143	152	122	—	Tub. peritonitis: absorpt. of fat = 72%
H.D.	3 „	14.10	113	146	120	113	100	Chronic intestinal indigestion.
G.L.	6 wk.	5.00	84	106	137	104	102	Biliary atresia.
M.B.	5 „	3.10	95	177	134	120	118	Biliary atresia.
M.M.	9 yr.	24.85	72	152	199	50	50	Catarrhal jaundice.

The fasting blood sugar is reported as being very variable but frequently low. The behaviour of the blood sugar after administration of glucose has been investigated by several authors. Fanconi³ reports varied results. Generally the rise of blood sugar after ingestion of glucose was very slight or even nil, but occasionally a normal or prolonged rise was noted. McLean and Sullivan¹⁵ obtained flat blood-sugar curves after 1.75 gm. glucose per kgrm. body weight, and in some patients even after as much as 9 gm. per kgrm. Administration of lvulose or galactose led also to no rise of blood sugar, although in two cases galactosuria was found. Thaysen¹⁶, and Thaysen and Norgaard¹⁷ report a subnormal rise of blood sugar after the ingestion of 1 gm. of glucose per kgrm. bodyweight.

In our series the fasting blood sugar was normal or subnormal, thus falling into line with the observations of other investigators. During the active stage of the disease, as indicated either by clinical manifestations or metabolic results, the administration of either glucose or lvulose led to an insignificant rise of blood-sugar. During a period of convalescence, resulting from dietetic treatment or otherwise, the blood-sugar curve becomes more normal in type. The low blood-sugar curve seems to be pathognomonic of the active stage of true celiac disease. In Table 4 are noted the values of the blood sugar curves found in six cases of non-celiac steatorrhea: in all the curve is normal in height. The abnormality in the curve therefore cannot be due to the excessive bulk of the intestinal contents.

The flat blood-sugar curve in celiac disease might be due either to an increased glycogenic function of the liver or to a greatly delayed intestinal absorption. It is unlikely that there is any increased glycogenic function since the low blood-sugar curve still persisted even when the patient was on a high fat diet. It is well recognized that such a diet raises the height and prolongs the fall of the blood-sugar curve. Accordingly the increase in glycogenic function should have been impaired; instead of this the blood-sugar curve was just as flat as when the subject was on a normal fat-intake. The rise of the blood sugar after subcutaneous injection of adrenalin was quite within normal limits, thus affording further evidence that as far as carbohydrate metabolism is concerned hepatic function is normal.

Thaysen¹⁶ has argued against defective absorption being the cause of the low blood-sugar curve on the following grounds. (1) The blood sugar is also lower than normal after intra-venous injection of glucose. (2) The R.Q. rises to about unity after ingestion of glucose. (3) The R.Q. is higher on a carbohydrate diet than on an ordinary mixed diet. He believes that the cause is some toxic effect on the endocrine glands. None of the objections advanced carry much conviction. No mention is made of change in blood volume after intra-venous injection of glucose and without information on this point it is impossible to determine whether the difference in blood sugar is due to disturbance in carbohydrate metabolism or to alterations in the concentration of the blood. It is possible that the diminished blood sugar is a result of the passage of a greater volume of fluid than normal from the blood stream. The evidence from the R.Q. results is also equivocal. First, it has been shown by Cathcart and Markowitz¹⁸ that the value of the R.Q. being really the resultant of all

the metabolic processes does not necessarily indicate the metabolism of any particular food material. Secondly, it is not denied that absorption of carbohydrate does take place. It is merely a delay in absorption that is postulated. Accordingly the fact that the R.Q. is raised during a high carbohydrate intake is evidence solely that more glucose is oxidized and not that it is absorbed as quickly as normal.

Thaysen and Norgaard¹⁷ hold the view that the abnormality in carbohydrate metabolism is due to some toxic effect on the endocrine glands. The evidence in support of this is a slightly hypernormal rise of blood sugar after the subcutaneous injection of epinephrine. In the few instances in which we have investigated the action of epinephrine we have found that the rise in blood sugar is quite normal when compared with the results obtained in normal children.

It has already been pointed out that the abnormality in glucose metabolism is not due to the bulk of the faeces mechanically impeding absorption. In this connection it is interesting to note the normal blood-sugar curve in a child suffering from tuberculous peritonitis in whom the percentage absorption of fat was much below normal. The defective utilization of fat was due to the blockage of the lacteals, leaving the intestinal epithelium unimpaired and thus allowing normal absorption of all blood-borne foodstuffs. In coeliac disease on the other hand it would seem that the intestinal epithelium or its immediate environment is at fault, so accounting for defective absorption of both fat and glucose.

Utilization of protein (see Table 5).—Herter¹⁹ concluded that although absorption of protein in coeliac disease is better than that of fat it is still not

TABLE 5.
SHOWING OUTPUT OF NITROGEN IN THE FECES.

Case No.	Intake of N. per day gram.	Nitrogen in faeces		
		Output per day gram.	As % of dried faeces	As % of intake
1 (iii)	3.521	0.305	2.0	8.7
(iv)	3.111	0.414	1.3	12.9
(v)	2.991	0.302	2.6	10.1
(vi)	3.939	0.154	2.6	3.9
(vii)	4.239	0.271	1.8	6.4
(viii)	4.135	0.230	2.0	5.6
2 (v)	5.998	0.235	1.2	3.9
(vi)	5.058	0.209	1.2	4.1
(vii)	5.617	0.271	1.5	4.8
3 (i)	3.760	0.711	4.5	19.0
(ii)	3.431	0.464	1.9	13.5
(iii)	3.617	0.550	1.7	15.2
(iv)	3.601	0.520	1.9	14.4
5 (i)	5.14	1.05	3.7	20.4
(ii)	3.81	2.04	5.5	53.5

as good as in health. Schaap¹² found that the percentage of nitrogen in the faeces was practically the same as normal : owing to the excess in the amount of faeces passed there was naturally a much greater loss of nitrogen than in health. McCrudden and Fales²⁰ maintain that the nitrogen in coeliac faeces is derived from the same source as in health, i.e., chiefly from the intestinal secretion. In one case a five-fold increase of nitrogen intake was actually accompanied by a reduction in the nitrogen content of the faeces. They conclude that the high faecal output of nitrogen in coeliac disease is due not to defective absorption but to re-excretion. Fanconi³, on the other hand, states that with rich protein intake relatively more nitrogen appears in the faeces both in normals and coeliacs. He gives figures which show that in mild coeliac disease about 16 to 20 per cent. of the nitrogen intake appears in the faeces, while in severe cases as much as 48·7 to 63·6 per cent. This is shown even more

TABLE 6.
CHEMICAL ANALYSIS OF BLOOD.

Case No.	Serum		Plasma	Blood		
	Calcium mgrm. %	Phos. mgrm. %	Fatty ac. as grm. tripalmitin per 100 c.cm.	Chlorine mgrm. %	CO ₂ vol. %	NPN mgrm. %
Normal			330-500	280-340	40-60	20-40
1	7·8	4·7	376	310	47·2	35·1
	—	—	405	—	—	—
2	7·7	3·0	354	340	57·6	—
	7·1	2·7	410	290	—	29·6
3	—	—	387	325	51·2	37·4
4	7·0	3·0	—	—	—	—
	6·3	2·0	—	—	—	—

clearly when the faecal nitrogen is computed as a percentage of the total excreted : in the normal this is 13 to 20 per cent. in the mild coeliac 19 to 27 per cent. : in the severe 43·7 to 52·1 per cent.

Our results show a much smaller percentage of nitrogen in the faeces than do those of Fanconi, probably because of the easily absorbable nature of the proteins (milk) given to our patients. The nitrogen percentage of the dried faeces seems to be quite within normal limits so that any excess in nitrogen loss must be the result of the great faecal weight. In three instances in our series a high percentage of nitrogen was found in the dried faeces : in these periods 19·4, 20·4, and 53·5 per cent. of the total intake of nitrogen was found in the motions. These results occurred simultaneously with a defective absorption of fat. It would appear, therefore, that in an acute stage of the disease the absorption of protein is hindered both relatively and absolutely, but not to the same extent as fat.

In two instances the ability of the patient to absorb urea from the intestine was tested : in both the excretion was normal both as regards time and amount. It seems, therefore, that whatever fault is in the intestinal utilization of nitrogen, it is not concerned with simple nitrogenous substances but with complex molecules.

Discussion.

The most striking feature in the chemical pathology of cœliac disease is undoubtedly the abnormality in the utilization of fat. All attempts to formulate a conception of the pathogenesis of the condition have been based on this abnormality. Generally speaking it has been held that the defect is one of absorption, but Moncrieff and Payne²¹ have tentatively suggested that the abnormality is one of defective intermediate metabolism, possibly a result of the impaired action of blood or tissue lipase. In a preliminary communication they have given figures for blood fat in cœliac disease which are in excess of those obtained from normal individuals. It is exceedingly difficult to obtain blood in different individuals when the intermediate metabolism of fat is at the same stage, as the various conditions affecting the migration of fat to and from the tissues are in great part unknown. We have estimated the blood fat in a few cases (Table 6), and have found all the values within the normal range which admittedly is a wide one. Fanconi³ reports low, normal, or even sub-normal values for the blood fat in the fasting condition. He further states that in cœliac disease the blood fat curve after oral administration of olive oil or butter is flatter than normal. These results indicate that whatever the state of intermediate fat metabolism the defective utilization is not the result of a high blood fat hindering absorption or promoting re-excretion into the gut.

Further evidence has been brought forward to show that carbohydrate is absorbed with more difficulty than normal. Another substance showing a defective absorption-curve is acid sodium phosphate (Fig. 2). On the other hand, oral administration of sodium chloride or urea led to the output of these substances quantitatively in the urine as speedily as in the normal individual. Methylene blue appeared in the urine as soon after ingestion as it did in the normal subject. It is possible that the apparently normal absorption of urea, chloride, and methylene blue may be due to the fact that these substances pass through the intestinal epithelium by the simple physical process of diffusion. Fat, glucose and protein probably require a more complex set of conditions such as narrow limits of pH, presence of bile-salts and so forth. It must be emphasized again that the defect in carbohydrate absorption cannot be attributed, unless in a minor degree, to the mechanical interference of the large amount of fat, since in the case of steatorrhœa due to tuberculous peritonitis the absorption of carbohydrate and protein was quite normal.

There is no evidence of any structural change in the intestine which could account for the grave defect in absorption. Lehdorff and Mautner²² sum up the post-mortem findings by saying that in general, the atrophy of the organs produced in cœliac disease is a result of the hunger condition. In two of our patients who died the pathological reports (for which we are indebted

to Dr. J. W. S. Blacklock), indicate that no abnormalities either macro- or micro-scopic were noted in the gastro-intestinal tract, while in only one was there atrophy of liver and spleen.

Freise and Jahr²³ attributed the defective fat absorption to an over-rapid passage of the chyme through the intestine. They have been able to increase the percentage utilization of fat by slowing the movement of food through administration of opium or atropine. Meyer²⁴ points out that fat-splitting also suffers as a result of increased rapidity of the passage of food through the bowel. In coeliac disease, however, fat-splitting is usually quite normal. In two cases we have followed the passage of a barium meal radiographically, but no abnormality was noted in the times taken to complete the various stages.

FIG. 2. Inorganic phosphorus content of serum after oral administration of NaH_2PO_4

Further, carmine or charcoal ingested orally did not appear any more rapidly in the faeces of the coeliac patient than in the normal. The improvement resulting from the administration of opium was probably due to slowing down of the passage of the chyme, thus allowing longer contact between food material and intestinal epithelium. The defect in coeliac disease is after all not an absolute one. The state of affairs might be compared to a catalytic reaction taking place in the presence of an insufficiency of catalyst.

It has been clearly shown that the abnormality is not present in the intermediate metabolism, nor can it be detected either in the intestinal epithelium or in the rate at which the intestinal contents pass. It would seem therefore that the fault lies in some physico-chemical abnormality of the intestinal contents.

The absence or paucity of bile in the intestine has long been suggested as the cause of the mal-absorption of fats in the coeliac state. The whitish colour of coeliac motions has been attributed to absence of bile products. These, however, can be demonstrated both in the fæces and the duodenum. It is generally held that the normal fæcal colour is masked by the excess amount of fat. Nevertheless it is quite possible that although the bile pigments are present, there may be a defective supply of bile-salts which, after all, for purposes of absorption form the all-important constituent of the bile. Miller, Webster, and Perkins²⁵ in 1920 published results of three cases treated by bile-salts. Unfortunately in only one case was a complete metabolic determination performed, and in it improvement was not marked as the child during the control period had commenced to improve spontaneously. The percentage absorption of fat was only increased from 85.8 to 87.0. In the other two

FIG. 3. Blood sugar curve in coeliac disease.

cases only the fæcal content of fat was estimated and this was certainly reduced with bile-salt treatment. The work, therefore, while strongly suggestive of the beneficial action of bile-salts on the absorption of fat is not conclusive. Fanconi³ could get no definite improvement by the use of bile-salt preparation (decholin). Bischoff²⁶, however, found that this substance led to an increased retention of fat and calcium: he could arrive at no conclusion as to the ætiological relationship between coeliac disease and bile-salt absence. Our own results are conflicting. In one there was definite improvement in fat and mineral absorption, but in the other there was quite a marked decrease in the retention of these substances. In one case (Fig. 3) the blood-sugar curve gave evidence of more normal carbohydrate absorption during the administration of bile-salts. Against the view that the absence of bile-salts is the important factor in the chemical pathogenesis of coeliac disease is the

great difference of the metabolic picture in states such as atresia of the bile duct where there is complete absence of bile. In such a condition the bulk of the phosphorus appears in the urine while the blood-sugar curve is quite normal in type. Administration of bile-salt in biliary atresia does not lead to increased retention of minerals (Table 7).

One other point brought out in the course of this series of observations seems to be the beneficial effect of acid sodium phosphate both on fat and mineral metabolism. It is difficult to believe that this benefit is the result of phosphorus as such, and it would seem probable that its action is due to its acid nature. It is now largely accepted that increasing the acid reaction of the intestinal contents leads to a better absorption of lime and phosphorus. Further, the production of bile is stimulated by secretin which is also the result of the action of acid on the intestinal epithelium. The administration of an

TABLE 7.

SHOWING EFFECT OF BILE-SALT ADMINISTRATION ON MINERAL METABOLISM IN A CASE OF BILIARY ATRESIA :
DAILY INTAKE, OUTPUT AND RETENTION.

Diet	Days	CaO (gram.)					P ₂ O ₅ (gram.)				$\times 100$		Retention gram. per kgm. body weight	
		Intake	Faecal output	Faecal output as soaps	Urin- ary output	Total reten- tion	Intake	Faecal output	Urin- ary output	Total reten- tion	Urine P ₂ O ₅	Faecal P ₂ O ₅		
											Faecal CaO	Faecal P ₂ O ₅	CaO	P ₂ O ₅
Cow's Milk 540 c.cm. + sugar gram. 24	5	0.837	0.8105	0.4290	0.0186	0.0079	1.161	0.4711	0.560	0.130	118.8	172.0	0.002	0.03
Cow's milk 540 c.cm. + sugar gram. 24 + sod. gly- cocholate	6	0.837	0.8061	0.6507	0.0128	0.0181	1.161	0.5303	0.5973	0.0337	112.6	152.0	0.004	0.008

acid salt should therefore favour both the absorption of minerals and the production of bile-salts. Verzàr and Kúthy⁸ have shown that the presence of bile-salts permit the absorption of soaps at an acid pH. In the absence of these salts the absorption of fats as soaps is impossible unless at a pH of 9.0. If accordingly the reaction of the coeliac intestine were alkaline, but not, of course, with as high a pH as 9.0, there would be a defective absorption of minerals and a defective flow of bile. Shift of the reaction to the acid side would thus facilitate the absorption of lime and phosphorus and simultaneously increase the amount of bile in the intestine thus raising the utilization of fat. If with the added amount of fat there is also absorbed more vitamin D, the fixation of the calcium and phosphorus in the bone would naturally follow.

Summary.

Summing up, it appears that the results obtained in metabolic investigations on cœliac disease may be at present best explained on the following assumptions :—

(a) The defect is one of absorption and is due to change or changes in the physico-chemical constitution of the intestinal contents.

(b) These changes probably include a shift of reaction to the alkaline side and a deficiency in the bile-salts.

(c) The poor retention of minerals is probably the result of the alkaline reaction of the contents of the gut together with a difficulty in vitamin D. Improvement in the retention of minerals may occur without synchronous improvement in fat absorption.

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APPENDIX.

Case 1.—W. B., male, was admitted to hospital on May 25th, 1927, at the age of 2 years and 10 months, with a history of diarrhoea and vomiting since he was 11 months old. He was small—wt.=8.68 kgm.—ht.=77 cm. (normal 87 cm.) with a prominent abdomen. The stools were large, pale and offensive. During residence in hospital diarrhoea continued with short periods of improvement. His weight on dismissal 10 months later (March 28th, 1928) was 7.36 kgm. Symptoms continued after dismissal and on May 14th, 1928, he was re-admitted. Weight was then 7.8 kgm. On Sept. 10th, he took diphtheria and later scarlet fever. He was removed to a fever hospital. On March 11th, 1929, one year and ten months after his first admission, he was re-admitted because of persistence of the diarrhoea. His weight was 8.61 kgm. He was dismissed 5 months later at the age of 5 years with a weight of 7.43 kgm.

Case 2.—E. A., female, was admitted to hospital when 4 years old with the following history: Healthy at birth but at 3½ months weighed only 6¼ lb. and motions were bulky and pale. This continued with occasional intervals of improvement of from 2 to 3 weeks. She was small and spare—wt.=8.48 kgm.—ht.=78 cm. (normal 96.7 cm.) with prominent abdomen. She was kept in hospital for 3½ months and stools continued pale and offensive with periods of improvement of from 1 to 3 weeks. On dismissal weight was 10.0 kgm. Five months later she was re-admitted because of return of diarrhoea and loss in weight. Weight on re-admission was 9.4 kgm. The attacks of diarrhoea became gradually less frequent, and on discharge one year later, when she was 5½ years old, the weight had increased to 14.18 kgm.

Case 3.—M. R., female, aged 4 years and 10 months, was admitted with a history of prominence of the abdomen and attacks of diarrhoea for 2 years. She was small—wt.=8.8 kgm.—ht.=78 cm. (normal 105.3 cm.) with a prominent abdomen. The stools were pale and bulky. She was kept in hospital for 6 months during which time diarrhoea continued with occasional periods of improvement. The weight on dismissal was 9.0 kgm.

Case 4.—J. S., male, was admitted on August 21st, 1929, when 2 years and 2 months of age. Except for a convulsion when 11 months old he thrived well until 1 year and 10 months, when attacks of vomiting and diarrhoea appeared and the weight began to fall. He was emaciated and dehydrated—wt.=5.95 kgrm.—ht.=75 cm. (normal 82.8 cm.). The stools were frequent, and green with numerous curds and much mucus. During residence in hospital there was but little gain in weight and the stools were frequently large, pale and offensive. Weight on dismissal 3 months later with measles was 6.65 kgrm. On Feb. 12th, 1930, he was re-admitted. He had made a good recovery from measles and had remained well until 2 weeks before re-admission when diarrhoea and vomiting returned, the stools being bulky and pale. He was emaciated—wt.=6.8 kgrm.—and Chvostek's sign was positive. Two weeks later carpo-pedal spasm appeared and was relieved with large doses of calcium chloride (30 grm. six times daily). Chvostek's sign reappeared on March 18th, and from April 2nd 2 pellets of radiostol were given twice daily.

FIG. 4. Case 4. Change in calcium and inorganic phosphorus content of serum during treatment with radiostol.

The behaviour of the calcium and inorganic phosphorus content of the blood serum during this period of treatment is shown in Fig. 4. It is of interest to note that both the calcium content and inorganic phosphorus content of the serum were low, a finding not uncommon in cases of rickets complicated by tetany, and that during treatment with radiostol there occurred a gradual increase in both. All clinical evidences of tetany disappeared in 2 weeks. Radiological examination of the bones showed no evidence of rickets.

The child continued to have large pasty motions, and on June 26th he took diphtheria and was dismissed, weighing 6.36 kgrm. He was re-admitted on August 6th and died suddenly within 24 hours. The post-mortem examination revealed atrophy of the spleen, liver and kidneys. here was no abnormality detected in any part of the stomach or intestines.

Case 5.—M. McC., female, was admitted on January 8th, 1930, aged $1\frac{1}{4}$ years. She had thriven well until 1 year old, when motions became pale and bulky, and she ceased to gain in weight. Weight on admission was 6·8 kgrm. and height 73 cm. (normal 74 cm.). Stools continued to be frequent, pale and bulky, and her weight fell steadily. On February 12th, 5 weeks after admission, when the weight had fallen to 5·3 kgrm. she died. Post-mortem examination revealed a few patches of broncho-pneumonic consolidation throughout the lungs. There was no atrophy of any of the organs. Irregular areas of congestion of the mucous membrane occurred throughout both large and small bowel.

Case 6.—A. F., male, aged 3 years. For 6 months previous to admission he had been losing weight, had vomited and had frequent loose motions. He was small and pale—wt.=11·14 kgrm.—ht.=78 cm. (normal 89·1 cm.). Stools were frequent, large and pale. He was kept in hospital for 5 months and attacks of diarrhoea continued with occasional intervals of improvement lasting 2 to 4 weeks. Weight on dismissal was 11·17 kgrm.

Case 7.—M. L., a private patient under the care of Dr. L. Findlay. The child was aged $3\frac{1}{2}$ and 4 years at the time of the two blood-sugar tests (Table 3).