Coeliac Disease - A Clinical and Biochemical Study, with special reference to Carbohydrate Metabolism and the Rôle of the Anterior Pituitary Lobe.

By

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C O N T E N T S.

PREFACE.

The investigations in this thesis were carried out in the Medical Wards and Biochemical Laboratory of The Royal Hospital for Sick Children, Glasgow, during the tenure of a Muirhead Scholarship. The research owes its initiation to Dr. Stanley Graham who has granted every facility for observation of the coeliac patients in his wards, and whose constant helpful criticism and suggestions have been greatly appreciated by the writer. To Dr Noah Morris for considerable help and advice in the biochemical work the writer is deeply indebted and for his kind co-operation in carrying out the fat metabolism analyses and blood N.P.N. estimations, the results of which he has permitted to be used freely in the text. The writer is also grateful to Professor G. B. Fleming for permission to investigate cases in his wards, and for his helpful criticism throughout the course of the investigation.

I. HISTORICAL SURVEY.

There is something of the spirit of adventure in probing the mysteries of coeliac disease. So many problems concerning it remain unsolved that an attempt towards elucidation of any one of these leads the investigator, unwittingly at times, to deviate frequently from the main path in the hope that here may lie the hidden secret, the true nature of the disease.

Previous investigators appear to have been governed by a like tendency as may be judged from the amount of emphasis laid on different features of the disease by different authors. It is now 46 years since Samuel Gee[22] first described the "coeliac affection" so graphically. The shortness of the paper in no way detracts from its value. Parsons[73] has rightly deemed it a classical clinical cameo which frequently forestalls the discovery of new facts, and he points out that later writers have added little to it as far as the clinical characters of the disease are concerned. In spite of the general nature of the survey Gee laid special emphasis on the chronicity of the indigestion, its relation to adult sprue, and the need for rigid dietetic measures if the patient was to be cured at all, for death, he added, was a common end. Gibbons[23] in his paper of the following year (1889), "The Coeliac Affection in Children," also struck/

struck the pessimistic note when he declared that most cases died. He denied Gee's statement that coeliac disease was closely related to sprue and thus started a discussion which is still being waged at the present day regarding these two points of view.

It was not till 1903 that any real advance was made in the appreciation of important features of coeliac disease. In that year, Cheadle[10] published his paper "On Acholia," in which he described six cases, five apparently suffering from coeliac disease and one from sprue. He was the first to recognise an excess of fat in the stools but came to the erroneous conclusion that their pallor was due to lack of bile. Subsequent articles by van Praagh[96] (1904) and May[54] (1905) relating to acholia lent support to Cheadle's view. At the same time Bramwell[5] was trying to establish as a clinical entity, a pancreatic form of infantilism. Some of the cases described were, as Miller and Parsons agree, undoubtedly coeliac disease. J. Thomson, writing on Infantilism in Allbutt and Rolleston's System of Medicine (1908) agreed with Bramwell but asserted that in some patients presenting a similar appearance and having a similar history of recurrent diarrhoea, the pancreas seemed to be functionally active.

Apparently unaware of Gee's and Cheadle's writings, Herter in America (1908) produced his monograph "On Infantilism/

Infantilism from Chronic Intestinal Infection."[33] He claimed that in five cases, presenting symptoms and signs which we now recognise as 'coeliac,' there was an absence of the normal bacterial intestinal flora and a replacement by Gram-positive organisms, chiefly B. bifidus of Tissier. What is of more importance to us in the light of our present knowledge of coeliac disease, however, is the fact that he was the first to furnish us with biochemical data. Faecal analysis showed a 30-40 per cent. fat content, three-quarters of which comprised fatty acids and soaps. He mentioned the existence of a negative calcium balance due he thought to the retention of calcium by the unabsorbed fat. Lack of development in these children he considered to be due to insufficient absorption of foodstuffs. He recognised also an intolerance to carbohydrate while protein was moderately well tolerated.

Still another descriptive title was given to coeliac disease in the paper by Heubner[35] (1909), "Schwere Verdaungsinsuffizienz." Thereafter the view began to spread that Gee's 'coeliac affection,' Cheadle's 'acholia' and Herter's 'intestinal infantilism' were one and the same condition. Hutchison[42] voiced this opinion and was inclined to believe that Herter was nearest the truth in that these cases were essentially examples of a chronic intestinal catarrh. Whether the Gram-positive organisms of Herter/

Herter were specific or secondary to the state of the intestine was, he thought, an open question. He maintained that there was insufficient evidence of an inactive liver but rather favoured a pancreatic lesion on the grounds that in some cases much unchanged fat was present, that there was an inability to digest starch, and thirdly, that pancreatic ferments by mouth were sometimes of benefit. Freeman[18] also was impressed by the relation of Herter's infantilism to Bramwell's type of pancreatic infantilism and he too obtained good results by the use of pancreatic extracts. Stimulated perhaps by the interest in gland extracts, Ostheimer[69] made an interesting observation on one case to the effect that treatment by thyroid extract for three months failed to cause any gain in weight but pituitary extract for one month produced a gain of two pounds. Too much stress cannot be laid on this statement, however, as it is well known that coeliac cases exhibit remarkably rapid rises in weight during the stage of convalescence without any drug treatment. I mention it merely as bearing on my investigations with anterior pituitary extract (see Sect. V).

Among the first to notice the association of tetany and steatorrhoea was Langmead[45] (1911). Two years later Parsons[70] demonstrated the first case on record of/

of rickets in coeliac disease. A wealth of literature has been the result of the recognition of these two complications of the coeliac affection. Tetany has been mentioned more particularly in relation to the adult form of the disease, non-tropical sprue or idiopathic steatorrhoea, especially by Radl and Fallon[76] (1932), and Bennett, Hunter and Vaughan[4] (1932), as well as in sprue itself by Bassett-Smith[2] (1919) and Barach and Murray[1] (1920). A detailed account of the bony changes in coeliac infantilism and their relation to rickets was given by Parsons[72] (1927). The work was elaborated by Hess[34] (1930) and as recently as 1933 F. J. Ford[17] investigated in this laboratory the metabolism of healing in coeliac rickets. The latter came to the conclusion that the rickets of coeliac disease was of the same nature as ordinary infantile rickets, though Parsons[73] pointed out that to obtain a cure treatment was usually necessary for a much longer time than for the cure of infantile rickets.

During the years of the European War, coeliac disease in England obtained a false popularity as it was one of the scheduled diseases for which extra meat was given. In spite of this 'epidemic' no new interpretation of the disease was forthcoming. In 1919, Cautley[9] demonstrated a case of coeliac disease to the London Medical Society. Analysis/

Analysis of the faeces revealed a total fat content of 44.4 per cent. (more than half of which was neutral fat) and an absence of bile pigments and urobilin. The urine was apparently normal except for an increased diastase content. Pancreatic extracts were of no avail and he came to the conclusion that the defect was in some way associated with the biliary functions: in other words, he was reverting to the view of Cheadle.

The work of Miller from 1920 onwards did much to throw light on this chaos of opinions. He was the first to stress the two-phase nature of coeliac disease, the stage of fatty diarrhoea and the non-diarrhoeic or quiescent stage.(56) He pointed out that even in quiescent stages the absorption of food fat was rather below normal, and preferred to speak of "some causative anomaly which, as it were, waxes and wanes rather than comes and goes." In conjunction with Perkins and Webster(56) he investigated the effect of bile-salts on fat absorption and the conclusion he came to was that bile-salts produced an improvement in fat absorption at the stage of fatty diarrhoea, while in the quiescent stage when the stools were comparatively normal their action was less evident. He denied the possibility of a pancreatic insufficiency as fat-splitting was normal and autopsy of one case showed no signs of pancreatic disease. What he did postulate was that/

that the excess of fat in the intestine might set up a transient enteritis to delimit further the fat absorption. A functional origin of the coeliac derangement appealed to him[57] as it was impossible to correlate coeliac disease with any type of organic hepatic disease and because cases of advanced hepatic disease did not present coeliac symptoms. In support of his view of a digestive fault rather than an organic disease he recorded a case two years later[59] whose autopsy revealed no abnormality of the intestinal tract and whose gall-bladder contained bile. This same case had exhibited during life symptoms of megacolon and Miller made the suggestion that some of the obscure examples of megacolon in children might be coeliac in origin. At a discussion on sprue and coeliac disease at the Royal Society of Medicine in 1924[61] he elaborated on his former views by stating that the liver seemed under chief suspicion and it was not unlikely that there was some abnormality in bile-salt secretion though no persistent inhibition of bile-flow. It is perhaps worthy of mention also before leaving Miller's work for the present that he and Perkins[58] were fully aware that the rare condition known as congenital steatorrhoea and the more commonly acquired pancreatogenic steatorrhoea were entities distinct from coeliac disease.

On the grounds that the symptoms and stool analysis of/

of sprue, coeliac disease and tabes mesenterica were similar Ryle[78] (1924) postulated an obstruction of the lacteals. His view has never been confirmed.

To preserve the chronology of this account one must record at this stage the conception of Schick and Wagner[82] (1923) that coeliac disease was a pluriglandular insufficiency, the evidence being based on a single autopsy. As subsequent post-mortem examinations have shown nothing to confirm their view it will serve only as an introduction to the endocrine theory, and further mention of endocrine relations will be reserved for the section dealing with the present investigations with anterior pituitary extract in coeliac disease.

Instigated apparently by the researches of Hill and Bloor[36] and Sperry and Bloor[86] on the relation of food fat to faecal fat in animals, Bauer[3] in 1928 and Fanconi in the same year[13] favoured a re-excretion of fat through the intestinal epithelium rather than a faulty absorption. Moncrieff and Payne[63] reported six cases of high blood fat and came to the conclusion that there was a mal-utilisation of fat with an excretion of fat from the blood into the faeces. The findings in this connection were contrary to those of later investigators, for example, MacRae and Morris[49] and Parsons.[73]

It is rather remarkable that no mention has so far/

far been made of any intensive research into the carbohydrate metabolism in coeliac disease. Suffice it to say that most workers were impressed by the intolerance to fats and regarded the carbohydrate intolerance as relatively unimportant. Howland in 1921,[40] however, believed the reverse and paid particular attention to the exclusion of carbohydrates till the last stage of his three-phase diet. He has a recent supporter in Morse.[65] Parsons has obtained the best results by a combination of the two views but stresses the fat intolerance. From 1929 to date there have been numerous investigations into the carbohydrate tolerance in coeliac disease by Thaysen, Svensgaard, MacRae and Morris, etc. These I purposely withhold here for full review later in the section dealing with this subject.

As regards the haematology, extensive work has been done by Fanconi[13] (1928), Strandquist[88] (1929), Thaysen[93] (1931), Vaughan and Hunter[97] (1932) and Bennett, Hunter and Vaughan[4] (1932). The last two references make particular mention of the occasional finding of a megalocytic anaemia which responds to treatment by marmite as well as liver. This fact coupled with the established existence of coeliac disease in adults by these same authors and others makes its differentiation from sprue a more difficult matter. Yet they (Bennett, Hunter and Vaughan) conclude with the remark that the two diseases are similar but separate entities, and in so doing/

doing agree with Miller and Parsons who are adamant on this point.

The question of vitamin deficiency has also been studied in coeliac disease. Parsons (1932) reviews the subject fully. Suffice it to say that there is no conclusive evidence of vitamin deficiency being a causal factor.

The present knowledge of the pathogenesis of coeliac disease is based on the recent publications of MacRae and Morris[49] (1931), Parsons[73] (1932), and Bennett, Vaughan and Hunter[4] (1932). All three papers impress the functional nature of the lesion; the first two stress changes of the physico-chemical constitution of the intestinal contents and the last prefers to make a more general statement of "a nutritional disturbance of gastro-intestinal origin dependent upon disturbance of function in spite of the absence of anatomical lesions." Detailed reference to their work will be given in following sections.

If the foregoing brief and rather incomplete survey has left the impression that very few avenues have not been explored in the search for an etiological factor in coeliac disease, it will have accomplished its object. By furnishing us with an accurate knowledge of the essentials in treatment, research has changed the pessimistic outlook of Gee and Gibbons to one of optimism by Haas[29] (1932), who heads one paper thus, "Coeliac disease - its specific treatment and cure/

cure without nutritional relapse." The virtue of the generally accepted line of treatment lies in a diet almost exclusively protein at first, carbohydrates being gradually introduced at a later stage and last of all, fats.

In the wake of this establishment of treatment on a logical basis, arrived at by scientific research, comes a startling publication by Pritchard[75] (1934) with views entirely opposed. On the strength of the hypothesis that bad feeding, especially an insufficiency of vitamins, is the causal factor or at least perpetuates the coeliac state, he condemns the restriction of fats and the limitation of carbohydrates including vegetables and fruits. Relapses, he considers, are due to the inability of the liver to cope with protein decomposition products and thus he advocates a minimum of protein foods.

Such unorthodox treatment requires further proof and only goes to show that the pathogenesis of coeliac disease still remains an unsolved problem.

II. FAT ABSORPTION IN COELIAC DISEASE.

"To give an entirely satisfactory definition of coeliac disease will not be possible until we know the actual cause of its essential feature, the mal-absorption of fat." So wrote Miller in 1926, and as pointed out in Section I most writers adopt the same attitude. It is fitting, therefore, to deal with this aspect first before going on to the question of utilisation of carbohydrates and proteins.

Previous Findings. Ever since Cheadle[10] in 1903 discovered an excess of fat in the stools, emphasis has been laid on the abnormal metabolism of fats in coeliac disease. Bramwell,[5] Hutchison[42] and several others attempted to explain the phenomenon by a deficiency of the pancreatic secretions as there was in some cases much unchanged fat in the stools. There was also an inability to digest starch and pancreatic ferments appeared to be beneficial. Herter[33] in 1908 was the first to show that a total fat content of 30-40 per cent. in the faeces was the rule in such cases, and three-fourths of that amount was composed of fatty acids and soaps. He advocated, therefore, that there was no diminution in the power of fat-splitting, the malabsorption being due to the presence of an enteritis.

In 1920, Miller obtained similar results to prove normal splitting of fats and further ruled out the possibility/

possibility of pancreatic deficiency by autopsy evidence. Later work led him to adopt the view of bile-salt impairment as a possible cause of malabsorption of fats but he added that the presence of fat in the intestine might accentuate the condition by causing a transient enteritis.

Ryle's view[78] (1924) of a lacteal obstruction did not find any supporters. Freise and Jahr[19] (1925) were of the opinion that the chyme was forced too rapidly through the intestine for efficient absorption and that administration of opium and atropine produced an improvement. MacRae and Morris tested this out in two cases by giving carmine and charcoal orally; these did not appear in the faeces more rapidly than in the normal individual. Also barium followed throughout the alimentary tract by X-rays showed no acceleration of its course.

The repeated negative post-mortem findings in the intestinal epithelium by Miller, Lehndorff and Mautner[51] and others directed the attention from this tissue regarding malabsorption of fat and other elements of diet.

Bauer,[3] Moncrieff and Payne,[63] and Fanconi[13] in 1928 were tempted to postulate a re-excretion of fat from the blood and no defect in absorption, the first two on the grounds that the blood fat was higher than normal and the last on the finding of an excess of fat output over fat intake. MacRae and Morris[49] estimated the blood fat in/

in a few cases and found all the values within a wide but normal range. Parsons in a series of careful experiments could find no evidence to support the theory. On the contrary he found a lower fasting blood fat and lower fat curves after olive oil in coeliac patients than in normal individuals. Furthermore he obtained a distinct relation between the composition of the food-fat and that of the faeces. One would expect a constant composition in the faeces in the case of re-excretion of fat from the blood.

Fanconi himself who supported the view gave low, normal or subnormal figures for the blood fat during fasting and flat blood fat curves after the ingestion of olive oil or butter.

On the strength of these facts, MacRae and Morris and Parsons dismissed the possibility of a defect in the intermediate fat metabolism.

Since their publications, Bennett, Vaughan and Hunter[4] have described the findings in a case of idiopathic steatorrhoea in a patient of 16 years first on ordinary hospital diet and then on low-fat diet (bananas, skim milk, fruit, green vegetables, bread and jam). On the low-fat diet the patient continued to pass 25 per cent. total fat in the faeces and the authors considered that these results would appear to support those of Fanconi but that interpretation of them at the present moment was impossible. There is one criticism to offer - the analyses of/

of fat content were made on single specimens of faeces, and moreover 25 per cent. is a subnormal value as compared with that of healthy subjects on ordinary diet.

MacRae and Morris[49] added several important data towards the appreciation of the fat metabolism in coeliac disease. Estimating the fat output in the faeces of several cases over periods of six to seven days they showed that the total fat in the dried faeces of patients on a low or normal fat diet averaged 42 per cent. (25.98-58.70). The figure in health is 33 approximately (See Hutchison[41]). Neutral fat formed less than one-quarter of the total fat, a figure well within the normal as reported by Hutchison[41] (1919-20).

Furthermore, the percentage absorption of fats where ordinary or low-fat diet was given was always below the normal figures of 94-98 per cent. but it bore a rough relation to the clinical condition of the patient, being lower at a less convalescent stage of the disease. Increase in fat intake was followed by an increase in absorption just as in normal children though the figure reached still remained below that of a healthy child. This has been confirmed by Parsons. Conflicting results were obtained with bile salts; there seemed to be an improved absorption of soaps, as these were diminished in the faeces. Acid sodium phosphate administration induced an increased absorption/

absorption of calcium and on the strength of this finding they postulated a shift to the alkaline side in the intestinal contents of coeliac patients. Besides preventing mineral absorption this change would inhibit the formation of 'secretin,' which is the result of the action of acid on the intestinal epithelium. This in turn would lead to an inhibition of the flow of bile. Now on the theory of Verzàr and Kuthy[98] (1929) in the absence of bile-salts the absorption of fats as soaps is not possible (in an alkaline medium) unless at a very high pH of 9·0. Hence through this alkaline shift and paucity of bile-salts there was defective absorption of fats and minerals.

In an attempt to investigate this problem of a possible bile-salt deficiency, Parsons[73] gave deoxycholic and dehydroxycholic acids to coeliac patients on basal diets and compared the fat balance with that prior to the test. No improvement in fat absorption was observed though he admitted that the number of experiments were too few. He quoted also the finding of Neale (1930) of a normal pH (6.9) of the intestinal contents of coeliac subjects. The latest view of Verzàr and Kuthy[99] that fat absorption occurs at an acid pH by the action of bile-acids on fatty acids rather than soaps would point to the presence of all the factors necessary for good fat absorption in coeliac disease. Yet Parsons summed up his opinion by/

by stating that although up to the present no change had been found in the intestinal secretions, there was probably a change of a physico-chemical nature in the absorptive mechanism of the intestine.

As will be gathered from a glance at previous findings in fat metabolism in coeliac disease there is a vagueness in the conclusions come to by various workers. This is attributed to the fact that the physiology of fat absorption and metabolism is still imperfectly known.

In concluding one might mention that the degree of atrophy sometimes seen in coeliac cases need not be due to malabsorption of fat, as Fleming and Hutchison[15] in 1924 pointed out that there was no defect in the power of atrophic infants to digest fat. Their view was confirmed by Parsons[71] (1924). Inanition seems to be concerned rather with a faulty intermediate metabolism of fats as pointed out by Graham and Morris[25] (1933).

The consensus of opinion then is that there is a defective fat absorption in coeliac disease the cause of which is not yet certain.

Personal Observations. During the past two years, twelve estimations of the fat metabolism in eight coeliac patients at different stages of convalescence have been made. The procedure adopted in each case was briefly as follows:- An accurately measured dietary of sufficient caloric requirements/

requirements was given and after a pre-metabolism period of three to four days, rectal lavage was carried out and the result discarded. Immediately following this the child was transferred to a metabolism bed and the faeces collected over a stated period, usually seven days, the final specimen of faeces being obtained by rectal lavage. Aliquot specimens of the diet were reserved daily for estimation of fat intake. After thorough drying of the faeces, the amount was weighed and the fats then extracted and estimated according to the method of Holt, Courtney and Fales.[37] The percentage fat absorption was readily determined from a knowledge of the output and intake of fat. The results are shown in Table I.

The figures agree with those obtained by previous investigators. The percentage fat absorption in all the cases was subnormal. Fat formed on an average 43 per cent. (22.39-56.38) of the dried faeces, i.e. roughly 10 per cent. above the finding in normal subjects, as reported by Hutchison[41] and Harrison and Sheldon.[30] Neutral fat comprised roughly one-eighth of the amount of total fat, indicating, if anything, a more thorough fat-splitting than the normal figure of one-third would suggest. MacRae and Morris put it at less than one-quarter in their series, while Bennett, Hunter and Vaughan's figures for 15 adults work out at roughly one-quarter. (The fraction would be smaller but for two high percentages of neutral fat, 42.2 and 45.2).

Case.	Age. (yrs)	Diet.
G.B.	$4\frac{8}{12}$	W.M. 1350 c Sugar 50 gr
H.B.	$4\frac{1}{2}$	W.M. Egg yolk.
B.G.	$3\frac{2}{12}$	2% M.1500 c Curds 260 g 2 bananas.
W.McK.	$2\frac{1}{2}$ $3\frac{2}{12}$	(a) W.M. 1500 c (b) " (c) W.M. 1800 c
D.McL.	$1\frac{10}{12}$ $2\frac{9}{12}$	(a) Curd M. 1440 c (b) C.M. +Banan 100 grm (c) W.M. 1440 c.
M.O'B.	$1\frac{8}{12}$	W.M.1200 c. S. 40 grm.
P.S.	$2\frac{10}{12}$	2% M. 1500 c.c.
J.W.	$2\frac{1}{12}$	W.M.1200 c. S.40 grm.

TABLE I.

Case.	Age (yrs)	Diet.	Date.	Total Wt. Dried Faeces. (grm.)	Daily Wt. Dried Faeces. (grm.)	% Total Fat.	% Neut. Fat.	% Free Fatty Acid.	% Comb. Fatty Acid.	Fat Intake (grm.)	Fat Output (grm.)	% Fat Absorption.	COELIAC CONDITION. Severity	% Exp. Wt.	Motion
G.B.	4 8/12	W.M. 1350 c.c. Sugar 50 grm.	18-25/4/33	118.00	16.86	40.07	9.830	13.72	16.52	45.09	6.754	85.0	++	76	Loose. 1-2 daily.
H.B.	4½	W.M. Egg yolk.	1-7/3/34	110.00	18.33	27.31	3.490	7.71	16.11	25.90	5.008	80.7	++	43	?
B.G.	3 2/12	2% M.1500 c.c. Curds 260 grm. 2 bananas.	29/9-7/10/33	147.80	18.47	45.08	6.070	15.45	23.56	46.88	5.640	82.2	++	59	Bulky. 1 daily.
W.McK.	2½	(a) W.M. 1500 c.c.	18-21/6/33	46.68	15.56	49.39	4.860	10.25	34.28	51.45	7.685	85.0	++	62	Good. 1 daily.
		(b) "	25/6-2/7/33	143.80	20.54	53.94	6.140	21.77	26.03	54.75	11.081	79.7	++	66	1-3 daily.
	3 2/12	(c) W.M. 1800 c.c.	1-7/3/34	273.00	45.50	56.38	5.160	40.75	10.49	70.45	25.643	63.6	+++	65	Oily; 2-3 dail
D.McL.	1 10/12	(a) Curd M. 1440 c.c.	27/9-4/10/31	65.50	9.36	43.42	1.127	11.30	30.99	27.08	4.063	85.0	++	56	1 daily.
		(b) C.M. +Banana 100 grm.	4-11/12/31	127.90	18.27	22.39	4.236	3.12	15.04	24.67	4.091	83.4	++	60	Constipated.
	2 9/12	(c) W.M. 1440 c.c.	27/8-3/9/32	62.39	8.91	55.50	5.001	16.41	34.08	50.56	4.947	90.5	+	60	Good. 2 daily.
M.O'B.	1 8/12	W.M.1200 c.c. S. 40 grm.	16-23/8/32	69.46	9.92	41.90	3.321	7.93	30.64	42.24	4.443	90.8	+	73	Constipated.
P.S.	2 10/12	2% M. 1500 c.c.	13-20/6/33	81.34	11.62	35.41	5.470	16.75	13.19	27.44	4.200	84.7	++	48	Constipated.
J.W.	2 1/12	W.M.1200 c.c. S.40 grm.	16-22/8/32	67.00	11.16	42.28	5.376	24.62	12.28	40.20	4.044	90.0	+	67	Occas. loose and undigeste

The thoroughness of the fat-splitting is in accord with the statement by Parsons[73] that specimens of pancreatic juice obtained by duodenal intubation have shown the presence of trypsin, amylopsin and lipase in normal amounts. Indeed, the latter was sometimes present in more than normal amounts.

The second feature brought out in this series is also confirmatory. MacRae and Morris found a relation between the clinical condition of the patient and the percentage fat absorption. The present figures bear out their statement for it will be seen that all those with a fat-absorption of 87.2 per cent. and under presented more severe symptoms of the disease than those with 90.0 per cent. or over. To display the same fact in a slightly different light, it is well known that in patients the subject of coeliac disease the bulk and frequency of the stools are an indication of the severity of the condition. A good response to treatment means fewer and less bulky motions. This being so, there should be an inverse ratio between the percentage of fat absorbed and the average daily weight of dried faeces. Figure I shows this fairly conclusively though it must be remembered that there are fallacies - the children are not all of the same age and their diets are different. Moreover, carbohydrates and proteins with their products account for a portion of the faecal output. In spite of this it appears more than a mere coincidence that the child with the poorest absorption/

absorption of fat (Case W.McK, (c).) passed the greatest amount of faeces daily. Case D. McL. at the age of $2^{1}/12$ years had a percentage fat absorption of 83.4 with an average daily excretion of 18.27 grm. faeces (dried): eight months later he was absorbing 90.5 per cent. of the fat intake and the daily weight of faeces had fallen to 8.91 grm. Though Table I does not include the metabolism findings in case P.S. after a period of treatment by anterior pituitary lobe extract, it may be mentioned here that the very high absorption of fats, 93.3 per cent., was accompanied by the lowest daily weight of dried faeces obtained in the present series of cases, viz., 8.22 grm. (See Section V, Table XXIV).

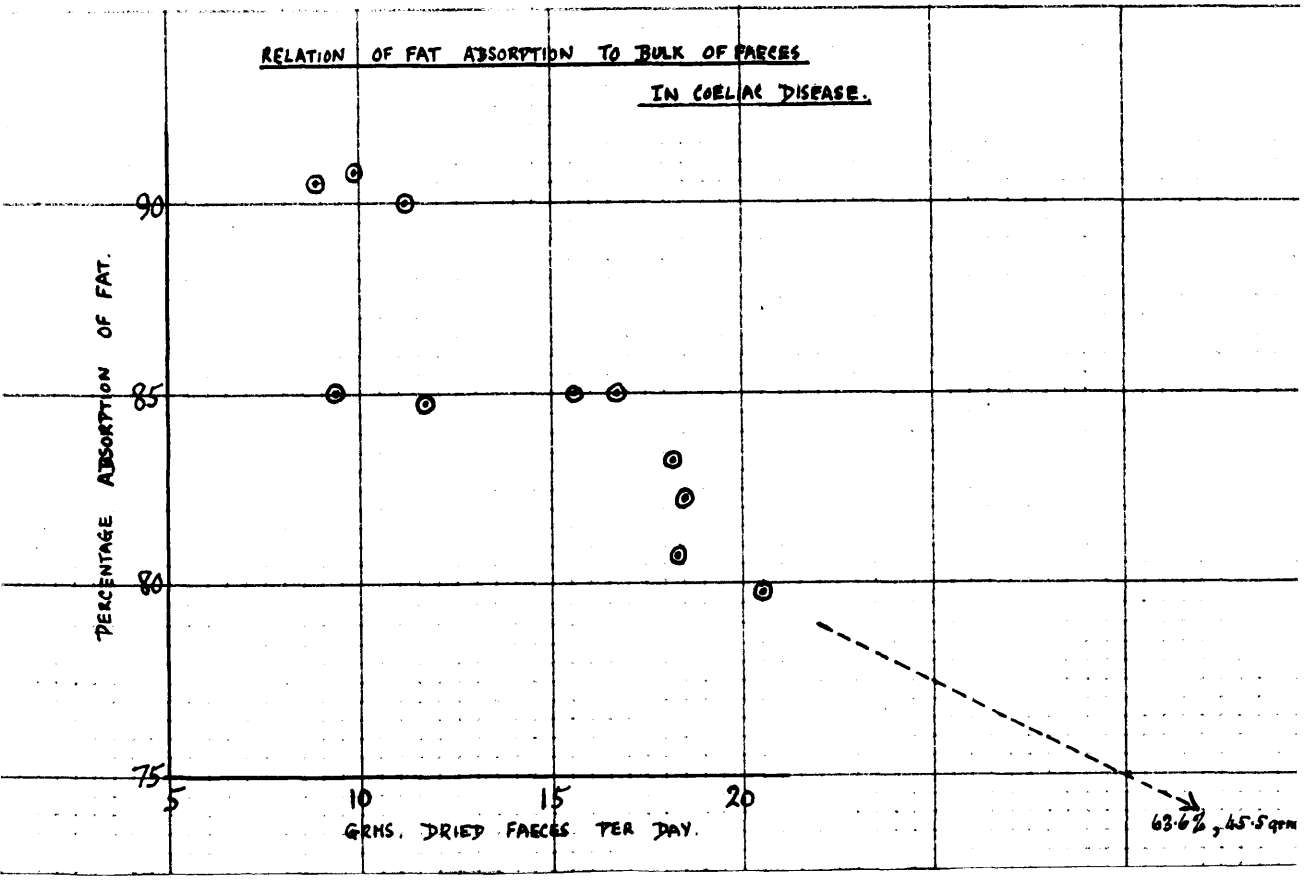


Figure I.

This lowering of the faecal output cannot be accounted for solely by an increase in the absorption of fats. It will be shown later (see Section III) that during convalescence the absorption of carbohydrates is also improved. Probably proteins are similarly involved though to a less extent for even in an acute stage of the disease protein absorption is moderately good.

The third feature of interest arising from the results contained in Table I deals with the varying proportions of soaps and free fatty acids - a question prompted by the view of Reginald Miller[60] (1923), that in the non-diarrhoeal phase of coeliac disease there is a predominance of combined fatty acids while in the diarrhoeal phase free fatty acids are in excess. Now, if Miller's opinion is correct one would expect that a high absorption of fats indicating a good period of the disease would accompany a high percentage of soaps. Accordingly the percentage fat absorption in each case was plotted against the percentage of combined fatty acids (soaps) to total fat in the faeces. The results were not so striking as one would have anticipated but the explanation is to be found in the fact that only in one instance was the fat metabolism estimated at the stage of frank diarrhoea. It can readily be understood that the length of the experiment and the difficulty of its application at such a stage rarely admit of its operation.

The/

The figures of Case W. McK. (c) therefore presented a valuable contrast to the others. Only 63.6 per cent. of fat was being absorbed while the faeces showed excess of free fatty acids, soaps forming only 19 per cent. of the total fat content.

At the other end of the scale, Case M. O'B. might be instanced with a fat absorption of 90.8 per cent. and a proportion of soaps as high as 63 per cent. When the results were divided into three sections as in Table II according to fat absorption figures (1) 60-70, (2) 70-80 and (3) 80-95, and compared with the corresponding percentages of soaps to total fat in the faeces, sufficient evidence was found to support Miller's theory, viz., the higher the absorption of fat the greater the proportion of soaps in the faeces. (See Figure II.)

Table II.

No.	Group % Fat Absorption.	Case	% Fat Absorption.	% Soaps/ Tot. Fat.
(1)	60-70	W.McK.(c)	63.6	19
(2)	70-80	W.McK.(b)	79.7	48
(3)	80-95	G.B.	85.0	41
		H.B.	80.7	59
		B.G.	82.2	52
		W.McK.(a)	85.0	69
		D.McL.(a)	85.0	71
		(b)	83.4	67
		(c)	90.5	61
		M.O'B.	90.8	63
		P.S.	84.7	37
		J.W.	90.0	29
Mean:			85.7	55

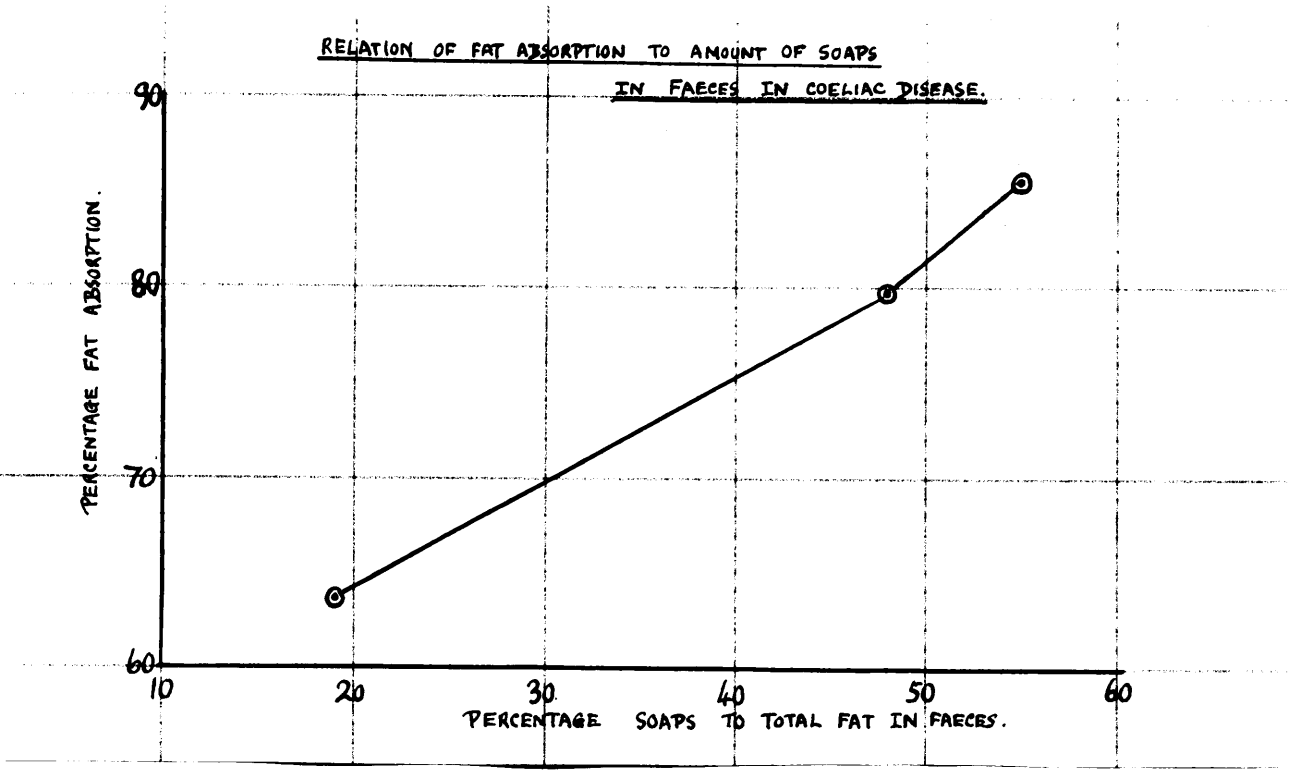


Figure II.

Finally, in closing this short study of the fat metabolism in coeliac disease, one finds in attempting to correlate the degree of nutrition and the ability to absorb fats that no such relation exists. Case P.S. though only 48 per cent. of her expected weight absorbed 84.7 per cent. of her fat intake, while case G.B. absorbed practically the same amount and was 76 per cent. of his expected weight. Again, it will be observed that case D.McL. happened to be 60 per cent. of his expected weight on two occasions when fat estimations were made at an interval of eight months. The fat absorption was not identical, being 83.4 per cent. the first time and 90.5 per cent. on the second/

second occasion. This finding was in accordance with the work of Fleming and Hutchison[15] (1924) and Parsons[71] (1924) who maintained that atrophic infants were as capable of digesting fats as normal infants.

SUMMARY OF FINDINGS IN SECTION II.

Twelve estimations of fat metabolism in eight coeliac patients revealed:-

(1) Defective absorption of fats - All below 94-98 per cent. as stated to be normal by Parsons.

Total fat comprised on an average 43 per cent. of the dried faeces (Normal figure 33).

(2) No defect in fat-splitting.

Neutral fat comprised one-eighth of the percentage of total fat (Normal figure one-third), indicating, if anything, therefore, a more thorough fat splitting than normal.

(3) Distinct relation between the percentage fat absorption and the clinical condition of the patient.

(a) At and under 87.2 per cent. absorption symptoms more severe than at 90.0 per cent. or over.

(b) Inverse ratio between percentage absorption of fat and daily weight of faeces.

(4) Relation between highest fat absorption figures and a high percentage of soaps in faeces.

(5) No relation between the percentage absorption of fats and the percentage expected weight of the patient (per se).

III. THE CARBOHYDRATE METABOLISM IN COELIAC DISEASE.

The intolerance to carbohydrates, particularly starch, has been recognised from the time of Herter as an important clinical feature. The characteristic frothy acid stools seen in severe cases are attributable to this metabolic fault and though most writers are agreed that the fat disturbance in coeliac disease is of primary importance, they are prepared to devote some attention to carbohydrates especially when the question of diet is being considered. Howland[40] in 1921 recognised the significance of the exclusion of this constituent of the diet when he refrained from introducing carbohydrate till the last stage of his three-phase dietary. It must be admitted, however, that the defect in carbohydrate metabolism has not so far proved such a fruitful source of help in attempts to arrive at the pathogenesis of coeliac disease as one might expect. One great difficulty has been the impracticable nature of carbohydrate balance experiments. The amount of glucose not absorbed cannot be accurately estimated in the faeces owing to fermentative changes in its substance. This accounts for the conflicting results of previous observers who have attempted investigations on these lines. McCrudden[51] found subnormal values for the lower fatty acids in the/

the faeces formed from carbohydrates, whereas Schaap[81] found a higher amount of faecal carbohydrate in coeliac disease than in other conditions.

Another method of approach to the problem was sought in the estimation of blood-sugar values.

Unfortunately there is such a complexity of factors at work in the regulation of the blood-sugar of the normal individual that when variations in values are obtained in the diseased organism one has to exert great caution in deciding which mechanism is at fault. Furthermore when determining the response to glucose ingestion in the normal child as compared to the coeliac patient it is absolutely essential to adopt the same standard of experimental conditions and technique. Neglect of these facts by early investigators led to wide differences of opinion as regards blood-sugar values in normal and diseased persons. Alterations in the previous diet, variations in the length of the fasting period, the amount of glucose ingested and the laboratory methods, etc., produced inconsistent figures.

A. BLOOD-SUGAR CURVES.

(1) Normal blood-sugar curve in children.

Svensgaard (1931) has dealt with this problem in a valuable review. Summing up the findings of previous authors she came to the conclusion that children who fasted four hours or more showed fasting blood-sugar values somewhat lower than those/

those of adults, i.e., under 90 mgrm. per cent. and usually 80-85 mgrm. per cent. She quoted the work of Sedgewick and Ziegler[83] (1920) who employed Folin's method in fifty breast-babies of 3 to 43 days old. The period of starvation was approximately twelve hours and they obtained an average fasting value of 80 mgrm. per cent. Greenwald and Pennel[26] (1930) also used Folin's micromethod in twelve tests on children 1 to 8 months of age and recorded an average fasting value of 80 mgrm. per cent. These results with Folin's method are comparable with those in the present investigation. The response to glucose ingestion on the other hand varied considerably with the method employed and the amount of glucose ingested. Svensgaard quoted the findings of Rumpf[77] and Herlitz[32] who used 1.3 gm. per kilo body-weight (Bang method and Hagedorn-Jensen method respectively) in children under one year and concluded that the rise was similar to that found in adults, the average maximum being 123-130 mgrm. per cent. (sometimes as high as 160 mgrm. per cent.) in a half to one hour after glucose ingestion, and the duration of hyperglycaemia less than 3 hours.

Employing the method of Hagedorn-Jensen and a fasting period of 5-6 hours in cases under 1 year, Svensgaard found lower fasting values (80-83 mgrm. per cent.) than in older children fasting 14-15 hours (88 mgrm. per cent.). Ingestion of 2 grm. glucose per kilo in the first series produced varying curves with an average maximum of 172 mgrm. per

cent. in 35 minutes and a duration of hyperglycaemia of less than two hours. Repeated curves on the same child on different days varied markedly. In another series of children of the same age-period, 1 grm. glucose per kilo. produced a less marked rise in blood-sugar (120-140 mgrm. per cent.). In children over one year given glucose 1.5 grm. per kilo, the results were more like adults and did not vary so much from day to day. The average maximum value was 155 mgrm. at 36 minutes and the duration of hyperglycaemia was also under two hours.

Personal Observations. The method employed, as in all subsequent investigations, was that of Folin and Wu, modified by Herbert and Bourne[31] (1931). In every case the period of starvation was approximately 10 hours. The blood obtained by pricking the thumb was collected in small tubes containing a minute amount of a mixture of potassium oxalate and sodium fluoride (10/1) to prevent clotting and glycolysis respectively.

Eighty-eight separate estimations of the fasting blood-sugar in normal children were obtained; some of these were estimations repeated on the same child where a series of sugar curves were carried out. For purposes of classification convenient age-groups were found to be 0-4 years, 4-8 years and 8-13 years:-

Table III.

Age Group.	0-4 yrs.	4-8 yrs.	8-13 yrs.
No. of estimations	18	38	32
Average fasting blood-sugar (mgrm. per cent.)	81.4	78.9	83.0
Extreme values	72.7-95.2	70.1-86.9	77.0-93.0

It will be observed that in the two lower age-groups, especially the second, the fasting blood sugar values tended to be lower than in the third. This is in accordance with Svensgaard's finding of higher values in older children, though it was under one year that she found the lowest values.

Ingestion of glucose (1 grm. per kilo) in 40 normal children gave the following average results:-

Table IV.

Age Group	No. of cases	Blood-Sugar. Mgrm. per cent.					Rise (mgrm. per cent.)
		Fasting	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	
0-4 yrs.	11	(72.7-90.0) 81.9	111.9	(111.1-146.0) 119.0	112.4	96.8	37.1
4-8 yrs.	15	(74.0-85.1) 78.8	128.8	(111.1-178.5) 131.4	112.6	84.4	52.6
8-13 yrs.	14	(78.4-93.0) 84.0	(123.5-194.1) 146.5	139.1	116.9	98.1	62.5

A much less significant rise in blood-sugar was noted in the lowest age-group than in the intermediate while an equivalent difference was observed between the intermediate and highest age-group. Thus, contrary to Svensgaard's statement, an adult type of curve was rarely found before the age of 4 years, was gradually approached in the next four years and became the rule rather than the exception after 8 years of age. The maximum rise in all three age-groups occurred at ½-1 hour after glucose ingestion while the duration of hyperglycaemia slightly exceeded 2 hours. These facts are clearly shown in Figure III.

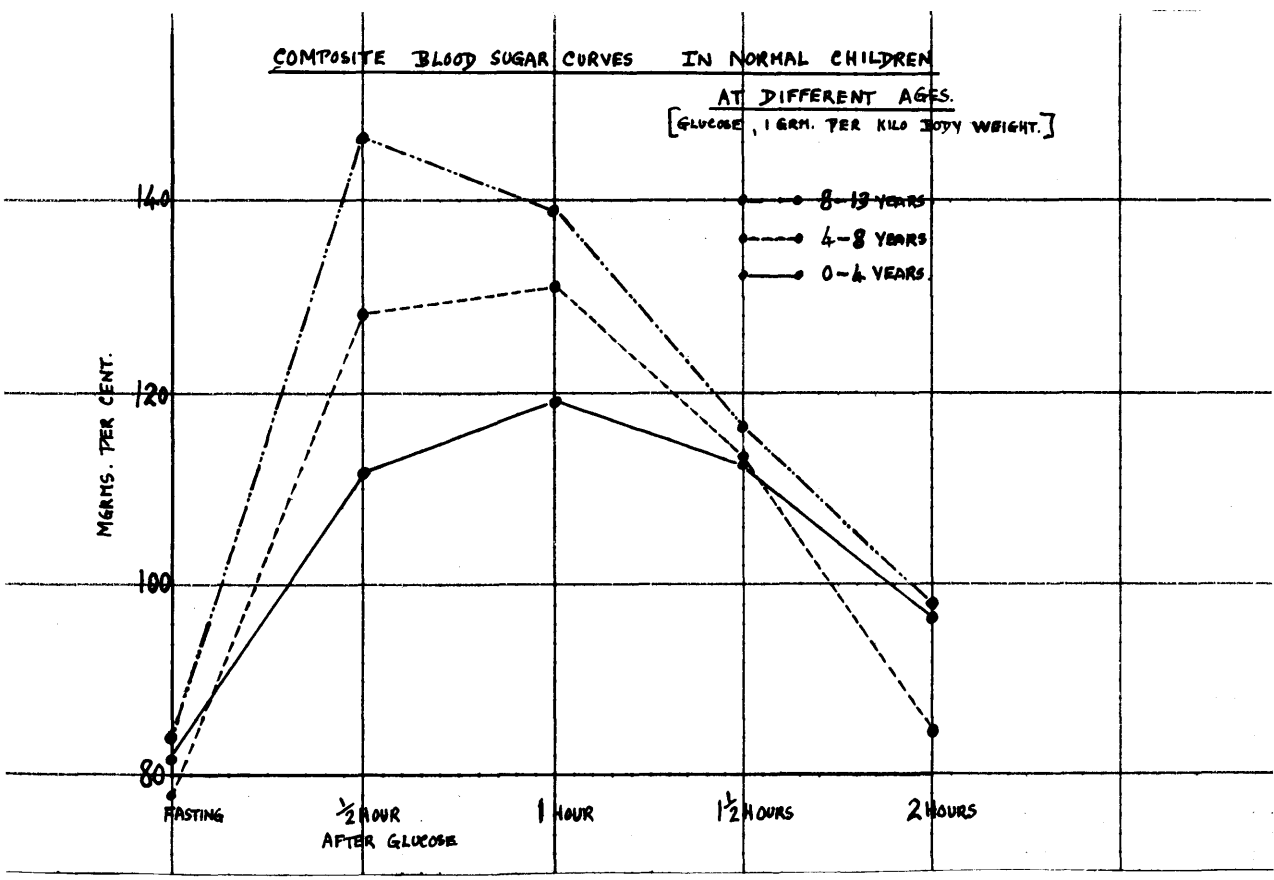


Figure III.

Ingestion of glucose in amount corresponding to 2 grm. per kilo body weight in 4 cases had the effect of heightening the curve and delaying its fall (see Table V and Figure IV). Herlitz[32] observed this same phenomenon and Svensgaard, though she did not obtain much variation in the duration of the hyperglycaemia also found higher maximum values than with 1 grm. per kilo.

Table V.

Amt. of Glucose.	Average Blood-Sugar. Mgrms. %					Rise. Mgrms. %
	Fasting.	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	
1 grm. per kilo Body Weight.	80.0	120.2	102.0	105.4	95.8	40.2
2 grm. per kilo Body Weight	92.9	133.1	155.4	139.9	114.1	62.5

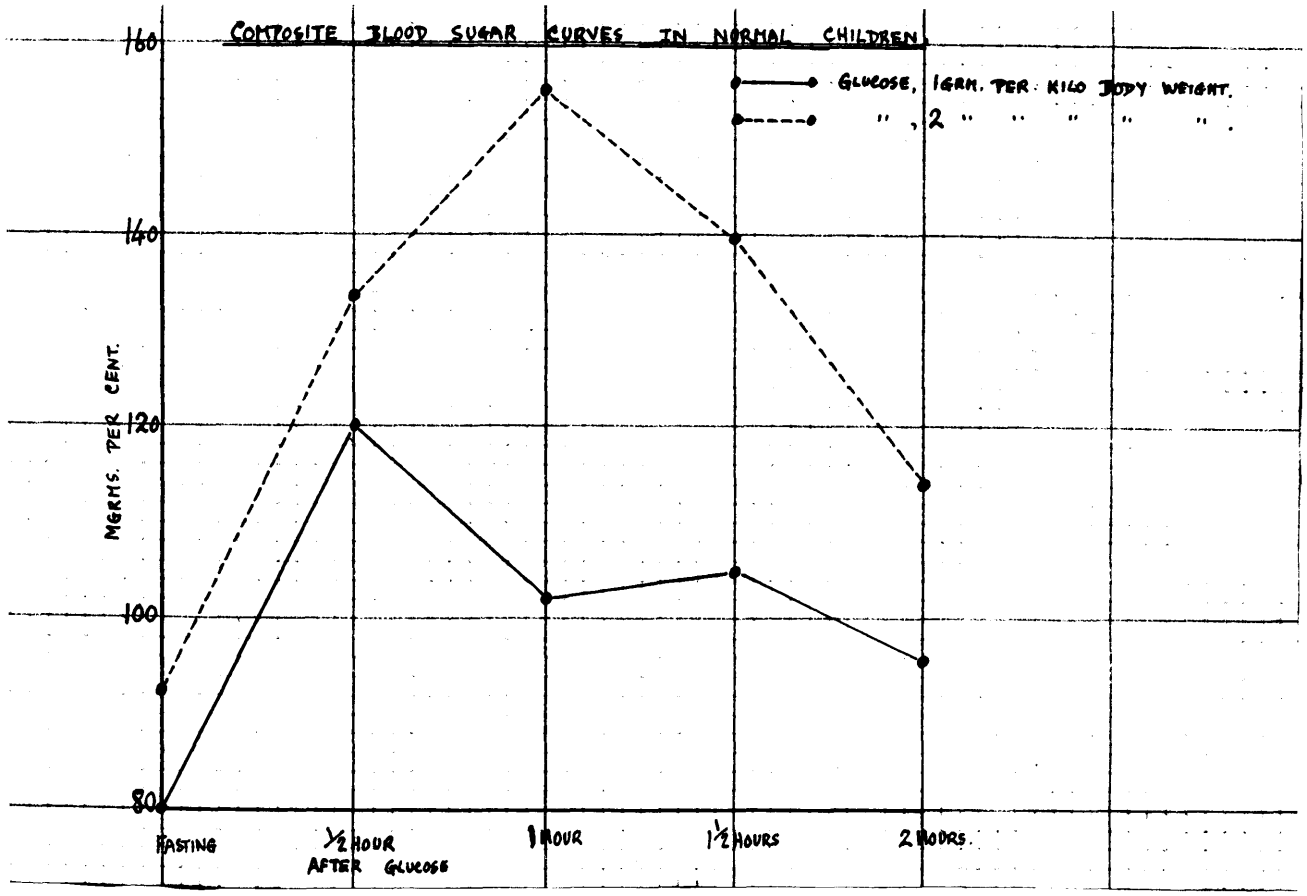


Figure IV.

(2) The 'Flat Blood-Sugar Curve' in Coeliac Disease.

The frequent association of coeliac disease with a flat blood sugar curve has been commented on by several observers in the past six years. Fanconi[13] in 1928 obtained in most instances an insignificant rise but occasionally a normal or prolonged type of curve. Fourteen cases investigated by MacLean and Sullivan[48] (1929) showed "an increased tolerance for dextrose." Amounts of glucose up to 9 grm. per kilo failed to elicit a rise of any consequence in some of their patients. Fasting blood sugar values varied from 66 mgrm. per cent. to 122 mgrm. per cent. Taking a rise of 40 mgrm. per cent. or less as evidence of a low blood sugar curve, Thaysen[91] (1929) found a subnormal rise of blood sugar in 10 cases of sprue and Gee-Herter's disease, but in two others who had almost recovered the curves were normal. In conjunction with Norgaard[92] he described the findings in 13 cases (1 grm. per kilo; Hagedorn-Jensen Method) at varying stages of convalescence. Low curves were irregular in their course with frequent after-rises, varied from day to day in the same patient, and were often noticeably shorter or longer than usual. Fasting values were frequently subnormal though rarely below 70 mgrm. per cent. Two cases showed a 'low-levelled' type of curve, i.e., where the maximum value was subnormal but more than 40 mgrm. per cent. above the fasting level, two gave higher curves with betterment in their clinical condition/

condition, and two who had recovered presented normal curves though the fasting values still remained slightly low. Svensgaard[90] (1931) reported normal fasting values but an exceedingly slight rise after ingestion of glucose (1-2 grm. per kilo) in five cases. No alteration in this finding resulted when tests were repeated at intervals of months or years so that she considered the flat sugar curve to be a valuable diagnostic sign of coeliac disease. MacRae and Morris[49] (1931) in a series of estimations in 6 cases found normal or subnormal fasting values. After ingestion of glucose (1 grm. per kilo body weight) these patients gave varying curves - low at an active stage of the disease and more normal in type during convalescence. Four subnormal curves with low fasting levels were charted by Parsons[73] (1932) to emphasise the common finding, while Bennett, Hunter and Vaughan[4] (1932) obtained in their adolescent cases eleven flat curves with subnormal fasting levels and two normal curves.

Personal Observations. Twenty glucose curves (1 grm. per kilo body weight) were obtained in seven patients with coeliac disease at widely different stages. In accordance with Thaysen and Norgaard and MacRae and Morris, the extremely flat curve was found only during the active stage of the disease. In convalescent periods the curve approached the normal type though many showed a delayed rise and fall, the/

the maximum value being reached only at 1-1½ hours after glucose ingestion. One case, J.W., in excellent condition clinically showed a remarkably high rise to 153.8 mgrm. per cent. in 1½ hours with a fall to 114.2 mgrm. per cent. at 2 hours. In all cases except one the fasting blood sugar was subnormal, being most commonly within the limits of 60 and 70 mgrm. per cent. but in 4 severe cases below 60 mgrm. per cent.; the lowest figure obtained was 41.7 mgrm. per cent.

Table VI.

Name.	Date.	Blood Sugar - Mgrm. per cent. Fasting	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm. per cent.	Clinical Condition.
G.B.	8.4.33	66.7	111.1	83.3	80.6	67.9	44.4	Good.
B.G.	18.12.31	60.6	104.1	66.6	68.8	62.5	43.5	Good.
	22.8.32	70.6	80.0	86.5	85.1	80.0	16.5	Poor. (Stools pale, offensive. Vomiting).
	10.1.33	74.0	105.2	93.9	90.0	71.4	31.2	Good.
	11.9.33	60.0	62.5	79.7	104.8	88.9	44.8	Good.
W.McK.	7.6.33	58.0	66.7	64.1	63.0	60.0	8.7	Poor.
	29.9.33	64.5	76.9	101.7	99.0	84.0	37.2	Moderately good.
D.McL.	9.9.31	61.0	67.0	68.0	63.0	67.0	7.0	Poor.
	20.8.32	50.0	52.6	58.8	57.7	50.0	8.8	Poor.
	13.1.33	73.5	76.0	103.6	77.0	77.0	30.1	Good.
	31.3.33	66.7	75.4	100.0	83.7	80.0	33.3	Good.
M.O'B.	9.8.32	83.0	85.0	100.0	95.0	70.0	17.0	Good.
	19.6.33	62.5	88.2	79.7	100.0	62.5	37.5	Good.
	9.10.33	64.5	100.0	85.1	86.9	74.0	35.5	Good.
P.S.	24.8.32	64.5	66.6	68.8	73.0	80.0	15.5	Poor.
	17.4.33	41.7	38.4	43.8	41.7	40.0	2.1	Very poor.
	22.6.33	50.0	60.0	65.2	54.5	43.5	15.2	Very poor.
	20.11.33	74.0	80.6	91.3	100.0	69.7	26.0	Good.
J.W.	9.8.32	73.0	74.0	76.0	74.0	71.0	3.0	Poor.
	3.6.33	71.4	108.1	139.8	153.8	114.2	82.4	Excellent.
AVERAGE CURVES:		58.6	63.2	66.4	64.0	61.4	7.8	Poor.
		66.5	105.1	82.2	81.6	68.9	38.6	Good.
		71.9	78.3	101.3	88.7	77.7	29.4	Good.
		65.5	77.1	83.6	101.6	73.7	36.1	Good.

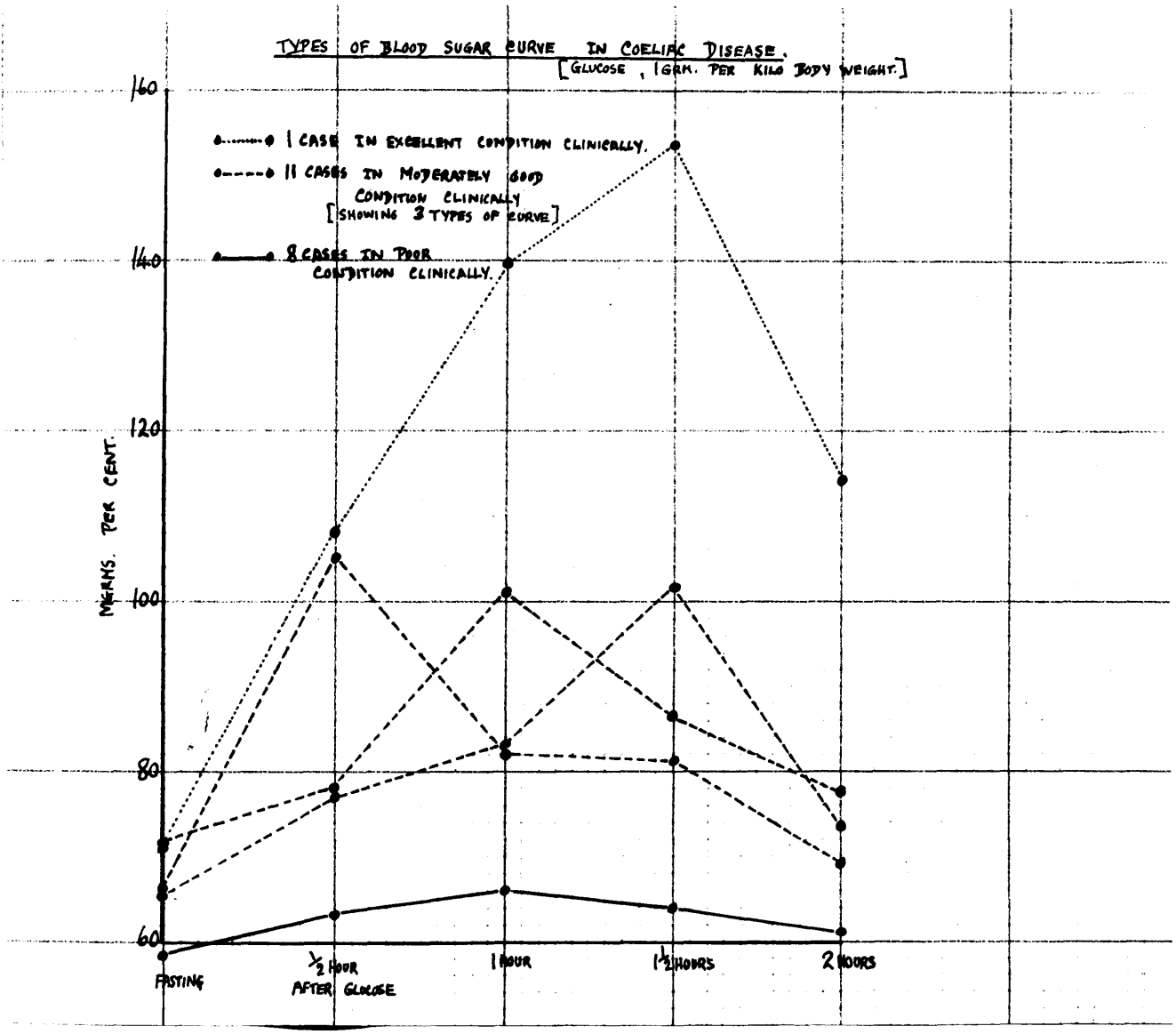

TYPES OF BLOOD SUGAR CURVE IN COELIAC DISEASE.
[GLUCOSE, 1 GRM. PER KILO BODY WEIGHT.]
1 CASE IN EXCELLENT CONDITION CLINICALLY.
11 CASES IN MODERATELY GOOD CONDITION CLINICALLY [SHOWING 3 TYPES OF CURVE]
8 CASES IN POOR CONDITION CLINICALLY.
MGMS. PER CENT.
160
140
120
100
80
60
FASTING
½ HOUR AFTER GLUCOSE
1 HOUR
1½ HOURS
2 HOURS

Figure V.

(3) The "Flat Sugar Curve" not Pathognomonic of Coeliac Disease.

Thaysen[91] (1929) noticed that a low blood sugar curve - that is, a curve with a rise of 40 mgrm. per cent. or less - was found as an inconstant phenomenon in about 5 per cent. of the blood-sugar curves of normal individuals. Jensen[44] (1930) investigating normal children of 8-11 years came to the conclusion that a low blood-sugar curve after glucose ingestion was no rare occurrence, though curves in steatorrhoea were more protracted and steady in their course than those in normal children. Again, in malnourished infants the frequent occurrence of a low fasting blood-sugar has been noted by several observers among whom were Guy[27] (1921) and Brown[6] (1925). Vomiting appeared to accentuate the condition while improved nutrition induced a rise in the sugar value. The response to glucose ingestion, 1 grm. per kilo., in these cases was found by Brown to be identical with that in the normal infant. A review of her results, however, reveals three flat curves in her series of marasmic cases and two amongst the cases of incorrect feeding.

Personal Observations.

(a) Malnutrition and/or Gastro-enteritis. Six undernourished infants under one year (one of whom had gastro-enteritis) and one well-nourished child of 18 months with enteritis/

enteritis exhibited flat curves after ingestion of glucose 1 and 2 grm. per kilo body weight (see Table VII).

Table VII.

Name.	Age.	Diagnosis.	Percentage expected weight.	Amt. Glucose: 1 or 2 grm/kilo.	Blood-sugar. Mgrm. per cent.					Rise. Mgrm. per cent.
					Fasting	½ hr. after glucose	1 hr.	1½ hrs.	2 hrs.	
P.McK.	4/12	Incorrect feeding.	61	1	77.2	102.5	81.3	79.3	82.6	25.3
M.T.	2/12	Incorrect feeding.	64	2	76.9	84.0	100.5	77.8	70.4	23.6
W.R.	3½/12	Incorrect feeding.	61	1	67.1	83.3	84.0	78.4	65.5	16.9
H.I.	3/12	Marasmus.	65	1	87.7	87.3	90.9	93.8	85.1	6.1
C.C.	4/12	Marasmus.	47	1	51.3	80.0	96.1	83.3	76.9	44.8
D.McV.	3/12	Gastro-enteritis.	66	2	67.8	105.2	81.9	75.5	88.8	37.4
M.S.	18/12	Enteritis.	100.0	1	60.0	60.7	60.0	75.0	75.3	15.3
Mean Curve:					69.7	86.1	84.9	80.4	77.8	16.4

(b) Cretinism. Four cretins given glucose 1 grm. per kilo body weight showed curves which might easily be interpreted as 'coeliac.' Svensgaard[90] (1931) was the first to record this type of curve in cretinism and she found that thyroid administration decreased the sugar tolerance./

tolerance. It is interesting to note that in the present series the nearest approach to a normal curve was obtained in case R.S. who had been treated with thyroid extract (three grains daily) for one week previous to the test.

Table VIII.

Name.	Age.	Amt. Glucose.	Blood-Sugar. Mgrm. per cent.					Rise in mgrm. per cent.
			Fasting	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	
I.G.	4 yrs.	1 grm. per kilo.	60.0	68.2	61.2	60.0	62.5	8.2
E.C.	$\frac{4}{12}$ yr.	1 grm. per kilo.	50.0	81.9	88.5	64.5	44.4	38.5
R.S.	3½ yrs.	1 grm. per kilo.	66.7	106.4	86.9	93.9	90.1	39.7
J.H.	$\frac{5}{12}$ yr.	1 grm. per kilo.	47.6	95.2	104.1	73.5	34.4	56.5
Mean:			56.1	87.9	85.2	73.0	57.8	31.8

In the light of these findings the value of the flat sugar curve as a diagnostic sign of coeliac disease becomes relative instead of absolute as thought by Svensgaard.

(4) Effect on blood-sugar curve of substituting 2 grm. glucose for 1 grm. per kilo during convalescent stage of coeliac disease.

In 1930 Svensgaard[89] described a case of coeliac disease aged 3 years 10 months, who had a flat sugar curve when 1.5 grm. and 2 grm. glucose per kilo were ingested but showed a normal curve with a rise of 77 mgrm. per cent. in 30 minutes when given 4 grm. per kilo. She concluded from this that by giving a larger dose of glucose it was possible to break through the barrier, whatever that might be, that prevented the blood-sugar rise. The patient was in an improved state of health at the time of the test with 4 grm. glucose per kilo body weight and in the light of my observations this constitutes the important factor.

Personal Observations. Two coeliac patients at a convalescent period presented sugar curves of normal or even supernormal dimensions when given glucose 2 grm. per kilo body weight, whereas the curves with 1 grm. per kilo were still slightly subnormal. In comparison with the composite curve obtained in normal children with 2 grm. glucose per kilo body weight (see Table V) these curves are really higher than normal.

It would appear, then, that during a convalescent stage in coeliac disease not only is fat absorption improved by an increased fat intake but also there is an apparently normal metabolic response to increased sugar intake.

Table IX.

Name.	Date.	Amt. Glucose.	Blood-Sugar. Mgrm. per cent. Fasting	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm. per cent.
B.G.	10/1/33	1 grm. per kilo.	74.0	105.2	93.9	90.0	71.4	31.2
	31/3/33	2 "	65.5	173.9	194.1	153.8	117.6	128.6
D.McL.	31/3/33	1 "	66.7	75.4	100.0	83.7	80.0	33.3
	30/3/33	2 "	67.7	133.3	194.1	166.7	97.5	126.4

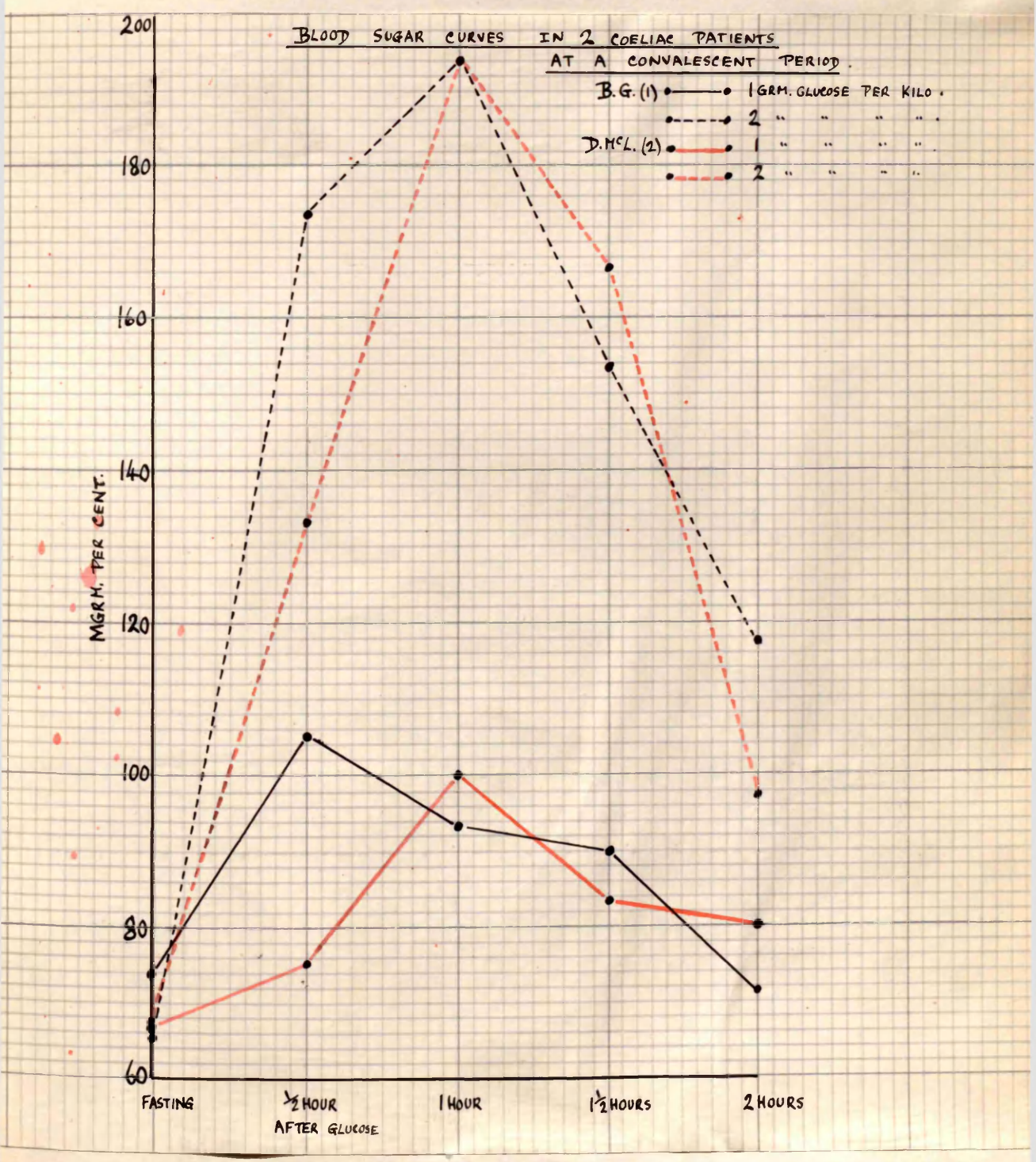


Figure VI.

To show that the same does not hold good when the coeliac symptoms are in evidence the effect of increasing the dosage of glucose was determined in a case who developed loose stools between the two sugar tests.

Table X.

Name	Coeliac Condition.	Date.	Amt.Glucose per kilo body wt.	Blood-Sugar. Mgrm. per cent.					Rise: Mgrm. %
				Fasting	½ hr after glucose.	1 hr.	1½ hrs.	2 hrs.	
G.B.	Pale, bulky stools.	8/4/33	1	66.7	111.1	83.3	80.6	67.9	44.4
"	Loose, frequent stools.	12/4/33	2	64.5	103.6	98.5	98.5	80.0	39.1

The rise with glucose 2 grm. per kilo body weight was slightly less though more prolonged than with 1 grm. per kilo.

B. LAEVULOSE CURVES.

Laevulose must be converted into glucose by the liver before being deposited as glycogen. In the presence of liver damage either unchanged laevulose or glucose passes into the blood stream and is not readily taken up by the muscles. Some observers have stipulated a depleted liver glycogen store in such cases, but the most recent view is that of Meyer[55] (1934) who suggests that in starved rats where liver glycogen stores are low, inability, not of the liver, but of the muscles to build up glycogen, is at least one factor of importance in an/

an excessive rise of blood sugar after laevulose. He does not dispute the finding of a high laevulose curve in liver cases, averring that the anabolism of glycogen in the muscles is influenced by the metabolic changes which carbohydrates undergo in the liver.

Whatever the mechanism involved, Brown[7] (1928) demonstrated that a rise in the blood sugar of 30 per cent. or more after laevulose ingestion was evidence of liver inefficiency whereas normal children rarely gave a rise higher than 15 per cent. Three coeliac patients in her series gave negative laevulose tests. MacLean and Sullivan[48] (1929) also found no rise in blood-sugar in coeliac subjects after laevulose or galactose though two demonstrated galactosuria. Svensgaard (1931) reported in one case a rise of 21 mgrm. per cent. after laevulose 1.5 grm. per kilo whereas with glucose in similar amount the rise was 20 mgrm. per cent. She considered it a negative test. Finally, MacRae and Morris[49] (1931) found an insignificant rise after laevulose during an active stage of the disease.

Personal Observations. Four coeliac patients were given laevulose 1 grm. per kilo body weight and the results compared with glucose curves obtained at the same stage of the disease. (See Table XI).

Name.	Condition.	
B.G.	Good.	1
W.McK.	Very good.	2
M.O'B.	Good.	2
P.S.	Good.	2
MEAN: (omitting W.McK		

Table XI.

Name.	Condition.	Date.	LAEVULOSE CURVE. (mgrm.%)					Rise per cent.	Rise in mgrm./ cent.	Date	GLUCOSE CURVE. (mgrm.%)					Rise in mgrm./ cent.
			Fasting.	½ hr. after laevulose.	1 hr.	1½ hrs.	2 hrs.				Fasting.	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	
B.G.	Good.	18/9/33	66.7	97.6	64.5	62.5	57.0	46.0	30.9	11/9/33	60.0	62.5	79.7	104.8	88.9	44.8
W.McK.	Very good.	27/9/33	63.7	68.0	64.1	65.7	66.7	7.0	4.3	29/9/33	64.5	76.9	101.7	99.0	84.0	37.2
M.O'B.	Good.	29/6/33	65.7	100.0	66.7	69.6	71.4	58.0	34.3	19/6/33	62.5	88.2	79.7	100.0	62.5	37.5
P.S.	Good.	24/11/33	60.0	66.7	84.2	73.5	68.1	40.0	24.2	20/11/33	74.0	80.6	91.3	100.0	69.7	26.0
MEAN: (omitting W.McK.)			64.1	88.1	71.8	68.5	65.5	46.0			65.5	77.1	83.6	101.6	73.7	

It will be observed that in three of the cases in Table XI the rise after laevulose was similar to that after glucose. Percentage rises of 40, 46 and 52 per cent. would lead one to suspect a mild degree of liver inefficiency rather than a depletion of muscle glycogen as the type of curve shows no delay in the return to normal. In fact the maximum is reached in ½-1 hour as compared with 1½ hours in the glucose curves.

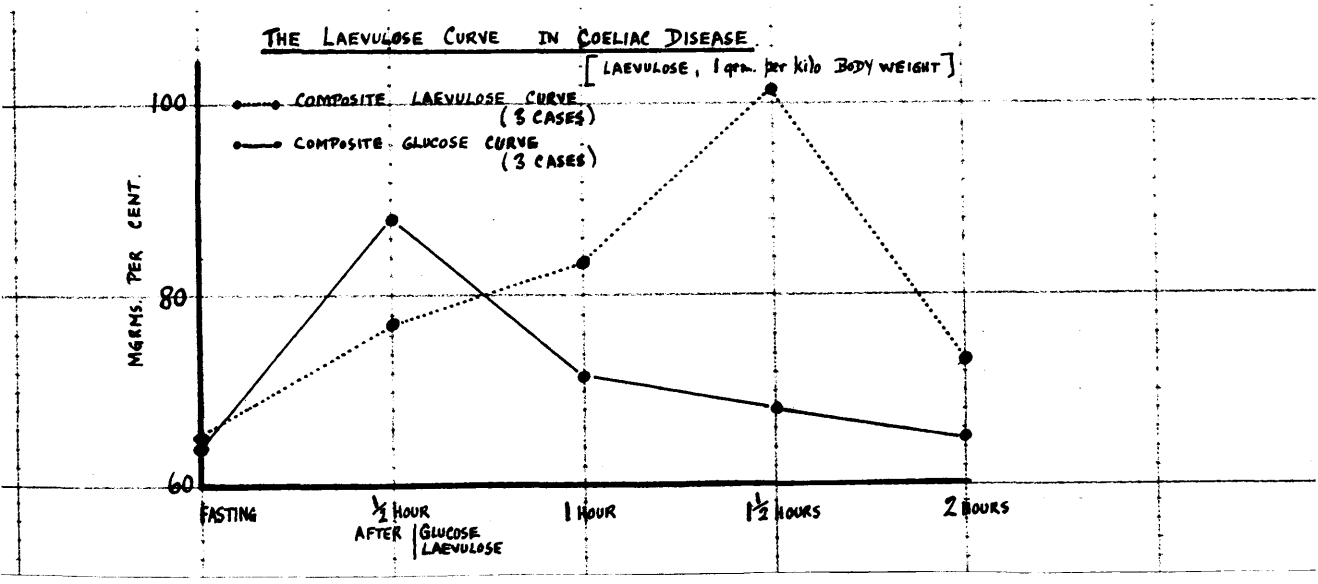


Figure VII.

Case W.McK. on the other hand showed an insignificant rise with laevulose and the association of this fact with a moderately high rise with glucose is difficult to explain unless one postulates that he had reached a stage where the liver deficiency had been temporarily cured though absorption from the intestine was not yet normal. It is worthy of mention that this case had just returned from a two months'/

months' stay in a convalescent home in the country where improvement had been marked. He had gained 1 lb. in weight and 3 cm. in height.

The question of a possible liver involvement in coeliac disease is merely touched on at this stage. It will be discussed fully after the study of further details in relation to carbohydrate metabolism.

C. THE UTILISATION OF INVERT SUGAR (RIPE BANANA) IN COELIAC DISEASE.

The value of the banana in the treatment of coeliac disease was first recognised by Haas[28] (1924) who maintained that it brought about a clinical cure in practically all cases. Whether there was a factor other than the sucrose content which was beneficial he did not know but since he instituted the treatment, the banana has remained one of the staple articles in the diet of the coeliac patient. MacLean and Sullivan[48] (1929) suggested that its virtue lay in the combination of the two carbohydrates, glucose and fructose, invert sugar being more normally metabolised than dextrose. Their statement was based on the finding in two cases that whereas dextrose produced a hypoglycaemic curve, the substitution of half the amount of dextrose by laevulose produced a normal curve.

Personal Observations. From Sherman's tables[85] one finds that the edible portion of a banana contains 22 per cent. carbohydrate or sucrose, which is composed of equivalent amounts of glucose and fructose. Accordingly an amount of banana with a dextrose content equivalent to 1 grm. per kilo was given to each of four normal children and four coeliac cases and the blood sugar estimated at the usual time intervals. The results were compared with the respective glucose curves (1 grm. per kilo body weight). (See Table XII).

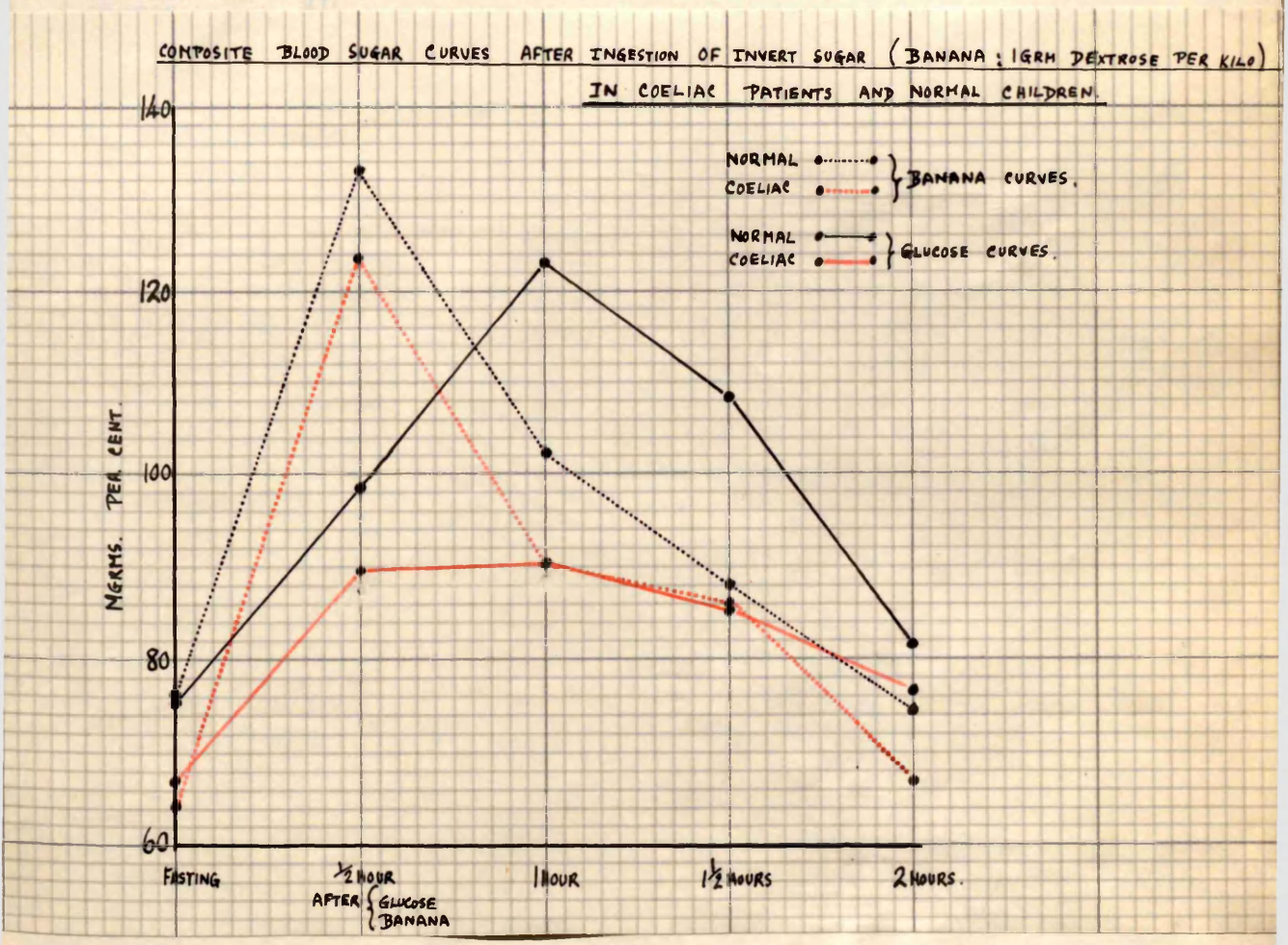


Figure VIII.

ORMAL CHILDREN.

se	Age (yrs.)	Diagnosis.	I
	7	Convalescent rheumatism.	1(
	4	Convalescent chorea.	1
	3	Infantile paralysis.	2
	3	Chronic appendicitis.	1,
		MEAN:	

ELIAC PATIENTS.

se.	Date.	Fasting	BA ½
.	30/3/33	64.5	
cL.	28/3/33	66.7	
'B.	27/6/33	67.7	
cK.	3/10/33	60.0	
MEAN:		64.7	

ORMAL CHILDREN.

Table XII.

se	Age (yrs.)	Diagnosis.	BANANA CURVE. (mgrm.%) Date.	Fasting.	½ hr. after banana..	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm./ cent.	GLUCOSE CURVE. (mgrm.%) Date.	Fasting.	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm. per cent.
	7	Convalescent rheumatism.	16/2/34	74.3	133.3	144.2	107.0	74.0	69.9	12/2/34	74.1	107.5	153.8	143.9	86.9	69.7
	4	Convalescent chorea.	14/2/34	76.0	133.3	93.0	80.0	73.4	57.3	12/2/34	74.1	100.0	111.1	105.3	81.6	37.0
	3	Infantile paralysis.	28/8/33	80.0	133.3	84.2	81.6	76.9	53.3	6/9/33	77.0	88.9	105.2	77.0	77.0	28.2
	3	Chronic appendicitis.	1/11/33	75.7	133.3	89.6	83.3	74.0	57.6		Not done.					
MEAN:				76.5	133.3	102.7	88.0	74.6	56.8		75.7	98.8	123.4	108.7	81.8	47.7

OELIAC PATIENTS.

ase.	BANANA CURVE. (mgrm.%) Date.	Fasting	½ hr. after banana..	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm. per cent.	GLUCOSE CURVE. (mgrm.%) Date.	Fasting.	½ hr. after glucose.	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm. per cent.
G.	30/3/33	64.5	68.9	100.0	86.9	65.5	35.5	10/1/33	74.0	105.2	93.9	90.0	71.4	31.2
McL.	28/3/33	66.7	133.3	80.0	80.0	74.0	66.6	31/1/33	66.7	75.4	100.0	83.7	80.0	33.3
O'B.	27/6/33	67.7	160.0	83.3	92.5	64.5	92.3	29/6/33	65.7	100.0	66.7	69.6	71.4	34.3
McK.	3/10/33	60.0	133.3	100.0	85.4	64.5	73.3	29/9/33	64.5	76.9	101.7	99.0	84.0	37.2
MEAN:		64.7	123.9	90.8	86.2	67.1	59.2		67.7	89.4	90.6	85.6	76.7	22.9

Although at a lower level in the coeliac patient the banana curve was found to be identical in contour and dimensions with that of the normal child. In each case the rise in mgrm. per cent above the fasting level was higher than in the corresponding glucose test but in the coeliac child the average difference in the height of rise was 36.3 mgrm. per cent. as compared with 9.1 mgrm. per cent. in the normal. It might be argued that if banana contains equal quantities of glucose and laevulose the sum of the blood-sugar responses to glucose and laevulose respectively in the coeliac patient might be equivalent to the response to banana. If the areas enclosed by the respective curves (see Figures VII, VIII) be considered the measures of blood sugar response it will be found that the area enclosed by the banana curve exceeds the added areas of glucose and laevulose curves. Hence the solution of the problem would appear not to be so simple and to depend rather on the inherent properties of invert sugar as a whole. The important fact remains that invert sugar is capable of raising the blood sugar of the coeliac subject to normal maximum heights whereas glucose (1 grm. per kilo) rarely does.

D. EFFECT OF FAT ON UTILISATION OF GLUCOSE IN NORMAL CHILDREN.

This investigation was carried out in an attempt to correlate the defect in utilisation of fats and carbohydrates in/

in coeliac disease. Jacobsen[43] in 1913, experimenting on six adults, found that the ingestion of 165 grm. white bread raised the blood sugar to 138-192 mgrm. per cent. whereas the same amount of bread with 85 grm. butter succeeded in raising it only to 116-155 mgrm. per cent. He concluded that either the fat formed an envelope to the particles of bread and prevented proper digestion by intestinal juices, or accelerated the passage of the starch along the intestine and did not allow time for proper digestion. Nassau and Schaferstein[66] (1926) investigating the effect of various foodstuffs on the absorption of glucose in normal children came to the conclusion that fat hindered it. Two years later Herlitz[32] pointed out that the results of these authors were fallacious because they had used different children as controls (glucose only) from those to whom they gave glucose and fat. Also the number of cases was too small to draw conclusions. However, the findings were in accordance with those of Fleming[14] (1922) who showed that in a case of biliary atresia a high fat diet lowered the respiratory quotient.

Evidence to support the opposite view has been brought forward by Brown[6] (1925) who gave to fasting normal and marantic infants a diet of lactose and water and compared the blood sugar curves with those obtained from a diet of milk with varying percentages of fat. She found that the curves were exactly similar in each case. Then Nissen[67] (1932) investigated blood-sugar curves in 16 normal children after intake of glucose 1, 2 and/

and 3 grm. per kilo respectively together with 2 grm. fat per kilo. He came to the conclusion that with 3 grm. glucose per kilo his results were similar to those obtained by Svensgaard with 1.5 grm. and 2 grm. per kilo in normal children without fat, and thus ingestion of fats together with carbohydrates did not influence the course of the alimentary hyperglycaemia. His conclusions cannot be justified on the grounds of such a comparison of results. It is unfortunate that he did not carry out glucose tests on the same group of children to whom he gave glucose and fat.

Personal Observations. Seven normal children of ages ranging from 4 to 10 years were given glucose 1 grm. per kilo in 80-100 c.cm. 40 per cent. cream after withdrawing fasting specimens of blood and the resultant blood-sugar curves compared with those obtained by ingestion of glucose alone. In each instance a considerable flattening of the curve was observed and in 4 of the cases the maximum level fell within the limits of 'coeliac' curves. (See Table XIII and Fig. IX).

E. EFFECT OF PROTEIN ON UTILISATION OF GLUCOSE IN NORMAL CHILDREN.

Nassau and Schaferstein[66] (1926) found that though fat and whey hindered carbohydrate absorption, white of egg had little effect.

Personal Observations. Five of the seven normal children previously mentioned were given glucose 1 grm. per kilo together with protein (a proprietary preparation, Protosol, was used) in amount $\frac{1}{2}$ grm. per kilo in 100 c.cm. water, and the blood sugar curves compared with those obtained with glucose alone. In four of these there was an insignificant fall in the maximal level while the last case showed a slightly higher rise. Protein, in other words, had little or no effect on the utilisation of glucose. (See Table XIII and Fig. IX).

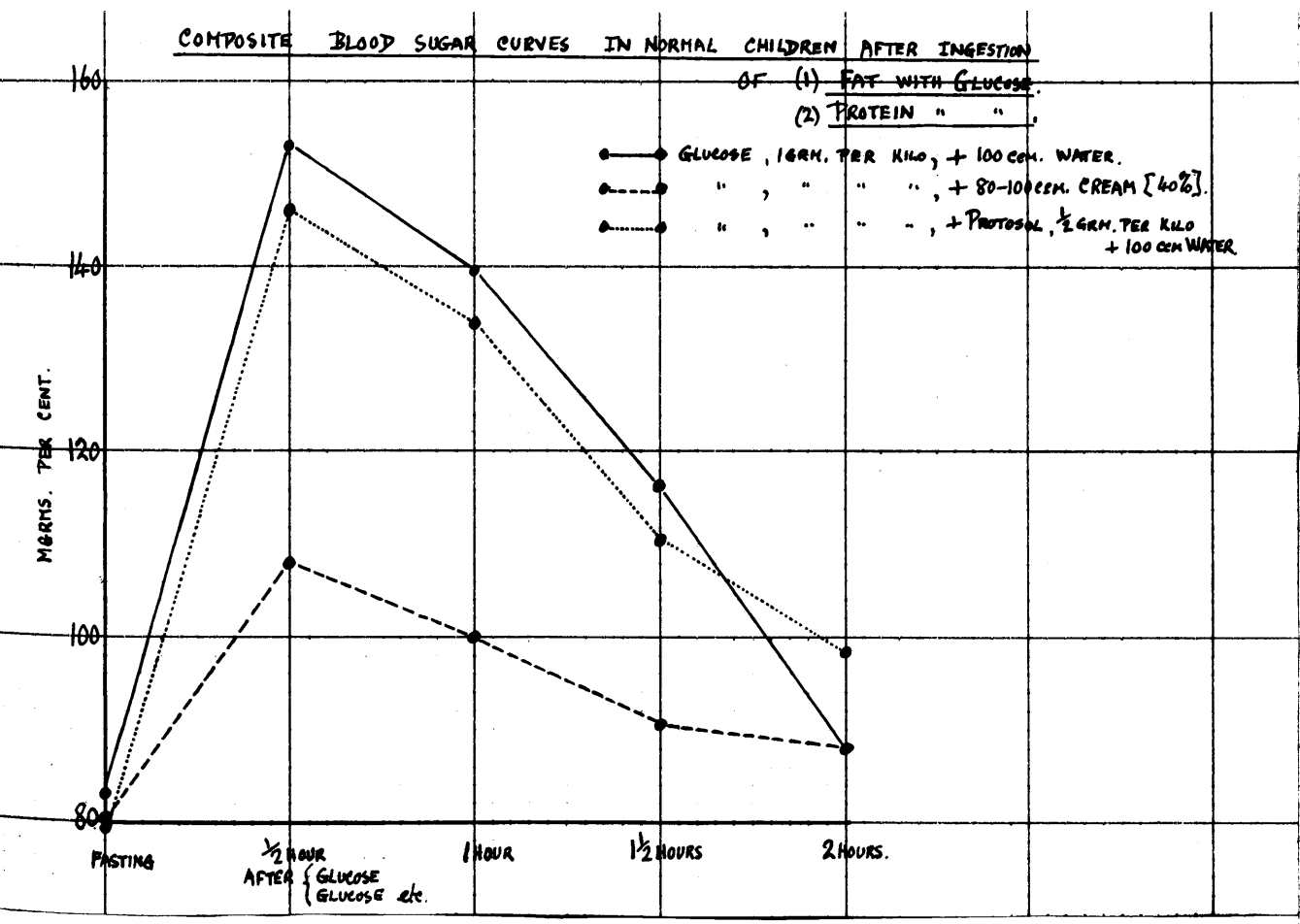


Figure IX.

Case	Age (yrs.)	Diagnosi
1	8	Convalescent Nephritis.
2	6½	Convalescent Pneumonia.
3	10	Convalescent
4	7	Lung Tumour.
5	4½	Convalescent Rheumatism
6	6	Convalescent
7	7	Chorea.
		MEAN:

Table XIII.

Case	Age (yrs.)	Diagnosis.	Blood Sugar. Mgrm. per cent.														
			Glucose 1 grm./k. in 100 c.cm. Water.					Glucose + 80-100 c.cm. 40% Cream.					Glucose 1 grm./k. + Protosol ½ grm./k. + Water 100 c.cm.				
			Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.
1	8	Convalescent Nephritis.	93.0	177.0	161.2	115.6	95.2	88.9	125.0	96.1	94.3	91.3		Not done.			
2	6½	Convalescent Pneumonia.	83.2	105.2	133.3	123.4	105.2	80.3	93.0	100.5	83.3	83.3	80.0	117.6	111.1	93.9	86.9
3	10	Convalescent Chorea	86.9	192.3	142.8	122.7	105.2	82.3	158.7	123.4	100.0	100.0	80.6	173.9	125.0	109.3	93.0
4	7	Lung Tumour.	80.0	150.3	133.3	117.6	83.3	80.3	93.0	106.6	90.9	86.9	80.0	117.6	142.8	121.9	95.2
5	4½	Convalescent Rheumatism.	80.0	153.8	176.9	142.8	66.7	80.0	80.0	100.0	107.0	86.9	80.6	151.5	148.1	106.4	95.2
6	6	Convalescent Chorea	74.0	166.7	117.6	109.3	78.4	70.1	95.2	83.3	76.9	83.3	77.2	170.8	144.9	122.7	122.7
7	7	Chorea.	84.0	129.0	111.1	86.9	83.3	83.3	112.3	93.4	84.0	83.3		Not done.			
		MEAN:	83.0	153.5	139.5	116.9	88.2	80.7	108.2	100.5	90.9	88.0	79.7	146.3	134.4	110.8	98.6

The application of these facts to coeliac disease where there is an excess of fat in the intestine normally would solve the problem of the flat blood-sugar curve, but for the fact that in cases of non-coeliac steatorrhoea it has been shown by MacRae and Morris and Svensgaard that the blood-sugar curve is normal. In support of their findings I insert here a normal curve from a case of acquired true steatorrhoea, probably pancreatogenic, whose percentage retention of fat was as low as 32·0.

Table XIV.

Case	Age (yrs.)	Diet.	Amt. Glucose	BLOOD-SUGAR. Mgrms. per cent.				
				Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.
H.C.	14	Milk, Rye Vita, Barley Sugar.	1 grm./ kilo.	81.6	108.1	153.8	129.0	115.6

SUMMARY OF FINDINGS IN SECTION III.

(1) The 'flat blood-sugar curve' is not a constant feature of coeliac disease but tends to become less flat in period of improvement.

One case in excellent condition clinically gave a hypernormal curve. The fasting level appears to remain slightly subnormal.

(2) The 'flat blood-sugar curve' is not pathognomonic even of the active stage of the disease, as similar curves are found in cases of malnutrition with or without gastro-intestinal disturbance and in cases of cretinism.

(3) During a convalescent stage increase in the dose of glucose from 1 to 2 grm. per kilo produces a normal or hypernormal curve.

(4) Laevulose curves in certain stages of the disease point to a mild degree of liver inefficiency.

(5) Invert sugar in the form of ripe banana is apparently absorbed as well by the coeliac as by the normal subject, although absorption as shewn by the glucose curve is not as rapid.

(6) Although in normal individuals the simultaneous ingestion of fat with glucose tends to lower the sugar curve, in coeliac patients the presence of an excessive amount of fat in the intestine cannot <u>per se</u> explain the flat sugar curve because non-coeliac steatorrhoea is associated with normal sugar curves.

EXPLANATION OF THE ABNORMAL CARBOHYDRATE METABOLISM.

Previous investigators have put forward various theories to support (a) a defect in absorption from the intestine, or (b) a faulty intermediate metabolism of carbohydrates. MacLean and Sullivan[48] (1929) after being careful to exclude a possible lowering of the renal threshold came to the conclusion that there was not sufficient evidence of a lack of absorption and rather favoured some endocrine involvement, possibly adrenal. Thaysen[91] (1929) attempted to rule out a defective absorption on the grounds that glucose intravenously also gave a flat curve and that the R.Q. almost reached unity after glucose ingestion and was higher on a high carbohydrate diet than on an ordinary mixed diet. His conclusions were criticised by MacRae and Morris as no mention had been made of a change in blood volume with intravenous glucose while the R.Q. estimations were not infallible on the basis set by Cathcart and Markowitz,[8] who showed that other constituents of the diet besides carbohydrate were responsible for the resulting R.Q. In view of the fact that they obtained a slightly hypernormal curve with adrenalin, Thaysen and Norgaard[92] postulated some toxic effect on the endocrine glands which regulated the blood-sugar content. Since then, however, MacRae and Morris and Svensgaard have found normal curves with adrenalin, while two of the cases in the present series showed/

showed a normal rise. Faulty absorption as a result of some abnormality in the intestinal epithelium or its immediate environment was the view adopted by MacRae and Morris. Parsons and Bennett, Vaughan and Hunter have also favoured defective absorption. On the other hand, Svensgaard in 1931, relying on her findings of higher sugar curves with larger doses of glucose, higher curves with glucose plus adrenalin than with glucose or adrenalin alone, and an increase of the respiratory quotient on ingestion of carbohydrate in one case, denied any error in the absorptive mechanism. She also ruled out an impairment of liver function with depletion of glycogen stores as adrenalin curves and one laevulose curve were within normal limits. The absence of any tendency to spontaneous hypoglycaemia was against a diagnosis of hyperinsulinism. She was inclined to the view that owing to the faulty metabolism of fat, carbohydrate utilisation was all the more rapid and suggested a possible hormone insufficiency.

Personal Conclusions. The abnormal sugar curve in coeliac disease would appear to depend on two factors:-

(1) Defective absorption from the intestine,
and (2) Faulty intermediate metabolism in the liver.

(1) Defective absorption.

(a) The lowest rise in the sugar curve is obtained in the acute stage of the disease when fat absorption is also much impaired. Higher rises are coincident with a stage of improvement when fat absorption is better.

(b) Increase in the dose of glucose from 1 to 2 grm. per kilo during a convalescent stage results in a normal or hypernormal rise of the blood-sugar. This is parallel to the finding by MacRae and Morris of an increased absorption of fat when the fat intake is raised during a period of convalescence.

(c) The occurrence of flat sugar curves in normal subjects when glucose and fat are ingested simultaneously coupled with the fact that normal curves are obtained in non-coeliac steatorrhoea would point to the conclusion that the presence of fat in the stomach and duodenum in health slows down the absorption of glucose by altering conditions possibly in the same direction as that in coeliac disease.

(2) Liver defect.

(a) The occurrence of a low fasting level of the blood-sugar.

This is in accordance with the hypoglycaemia obtained by partial or complete removal of the liver in dogs by Mann and Magath[53] (1927): secondly, the low sugar level in derangement of the liver function by experimental ketosis (Gilchrist, M.L.[24] (1932)): and thirdly, the spontaneous hypoglycaemia associated with hepatitis (Moore and O'Farrell[64] (1934)).

(b) The tendency towards a prolonged rise and delayed fall in some of the sugar curves obtained during convalescence.

The hypernormal lag curve found in one case who presented the best state of nutrition is also typical and similar to the curves shown by Gilchrist in ketosis in normal children. Some regard must be had, however, to the diet of the children at this stage, as prolonged protein feeding might conceivably lead to glucose intolerance.

(c) The occasional occurrence of a positive laevulose curve.

A feasible solution to this problem is that in the/

the acute stage of the disease absorption of laevulose is so poor that an insufficient amount reaches the liver to show up the liver defect. When absorption improves during convalescence the positive laevulose curve asserts itself. The ideal third stage would be where absorption is good and the functional liver defect had passed off: in such a position one would expect an insignificant rise in blood sugar after laevulose ingestion. Case W.McK. in Table XI may presumably be considered to have reached such a stage.

IV. PROTEIN METABOLISM IN COELIAC DISEASE.

The first comment on any defect of protein metabolism in coeliac disease was made by Herter[33] (1908) who recognised that there was a diminished absorption of proteins though to a less degree than fats. McCrudden and Fales[50] (1913) from the results of a single case were inclined to the view that the increased nitrogen loss was due to a re-excretion into the colon. Schaap[80] (1923-1926) found a normal nitrogen content of the faeces and affirmed that the high figures reported by other workers were due to the excessive bulk of the stools. High faecal nitrogen figures were also recorded by Friese and Jahr[19] (1925) and Lehndorff and Mautner[51] (1927), while Fanconi[13] (1928) showed that the coeliac subject excreted up to 50 per cent. of nitrogen in the faeces whereas the normal child gave figures of 13 to 20 per cent. MacRae and Morris[49] (1931) reported a much lower percentage loss, due, as they pointed out, to the ease of digestibility of the food-proteins (milk) given to their patients. In three cases 19.4, 20.4 and 53.5 per cent. respectively of the total nitrogen intake was found in the motions and these higher figures coincided with periods where there was a markedly defective fat absorption. Hence they concluded/

concluded that food nitrogen was badly absorbed in the acute stage of the disease but not to the same extent as fat. With a simple nitrogen compound such as urea it was found that absorption and excretion were normal. This further supported their opinion that the defect of protein metabolism was concerned more especially with the complex nitrogenous substances.

Parsons[73] (1932) found in four cases during a non-diarrhoeal period of the disease that nitrogen absorption was quite satisfactory, the percentages excreted being 5.2, 7.3, 11.8 and 15.5. Bennett, Vaughan and Hunter[4] (1932) in their adolescent cases did not carry out balance experiments but they remarked on the frequent low figures they obtained during observations of the blood urea and N.P.N., viz., 16-35 mgrm. per cent.

(1) <u>The N.P.N. Curve after Urea Ingestion.</u>

Using the micromethod of Folin and Svedberg,[16] Tindal[94] (1933) found in this laboratory that in normal children, aged 4 to 12 years, the fasting N.P.N. of the blood lay between 18 and 40 mgrm. per cent., while after ingestion of urea 15 grm. in 100 c.cm. water the level reached an average maximum of 51.4 mgrm. per cent. at 1 hour and fell to 44.9 mgrm. per cent. at 2 hours. In all cases the curve was on the downward trend at 2 hours.

Hepatic/

Hepatic disease, on the other hand, was associated with a higher fasting level, 26.7-52.6 mgrm. per cent., and a delayed rise to a high level at 2 hours (average 69.2 mgrm. per cent.) and 3 hours (average 63.3 mgrm. per cent.). In no case was the curve reverting towards the fasting level at 2 hours and in three cases out of 13 the curve was still rising at 3 hours. By 4 hours all had begun to descend. She concluded that the high fasting level was evidence of the inability of the liver to store the end-products of endogenous protein metabolism. The delayed rise showed defective absorption from the bowel and the prolonged high rise pointed also to a defect in liver retention. The test was regarded as a useful gauge of hepatic efficiency.

Yet hepatic disease was found by the same author not to be the only malady showing this type of N.P.N. curve. Coeliac patients gave exactly similar curves (unpublished - see Thesis, 1933).

Personal Observations. Eight N.P.N. curves were carried out in seven coeliac patients under the same experimental conditions as Tindal employed, i.e., after fasting overnight the child had a specimen of blood withdrawn from the finger and was then given 15 grm. urea in 100 c.cm. water flavoured with 30 c.cm. syrup of lemon. Blood was collected at ½, 1, 2 and 3 hours after urea ingestion. The same method of estimation was used - viz., that of Folin and Svedberg.(16)

Table XV.

Case.	Diet.	Date.	N.P.N. - mgrm. per cent.				
			Fasting.	½ hr. after urea.	1 hr.	2 hrs.	3 hrs.
G.B.	Ordinary diet.	17/4/33	34.2	45.4	57.4	62.5	54.9
	Milk - Sugar.	27/4/33	37.0	38.4	43.4	45.4	62.5
B.G.	Butter Curd Mixture. Curds. Bananas.	20/11/31	52.0	58.7	100.0	111.0	100.0
W.McK.	Light Diet.	14/6/33	34.7	55.5	66.6	73.5	78.1
D.McL.	Butter Curd Mixture. Curds. Bananas.	20/11/31	39.0	50.0	55.0	55.0	92.0
M.O'B.	Sweet Curd Mixture. Curds. Bananas.	24/6/33	38.4	62.5	96.1	90.9	83.3
P.S.	2% Milk. Bananas.	25/4/33	41.7	55.5	50.0	57.5	67.5
J.W.	2% Milk. Curds. Bananas.	7/6/33	26.7	40.0	45.4	50.0	62.5
MEAN:			38.0	50.8	64.2	68.2	75.1

In agreement with Tindal's findings and unlike those of Bennett, Hunter and Vaughan, one obtained fasting levels of the blood N.P.N. slightly higher than normal, 26.7-52.0 mgrm. per cent. The curves rose to high levels at 2 hours and 3 hours, in five instances still continuing to rise at 3 hours. It is noticeable from Figure X that no delay in absorption of the/

the urea occurred, a fact which supports the opinion of MacRae and Morris in their balance experiments. In this respect, also, the N.P.N. curve in coeliac disease differed from that in hepatic disease where the absorption of urea was shown by Tindal to be delayed.

Worthy of mention is the fact that in the case of J.W. (Table XV) the typical urea curve was obtained at a period when glucose ingestion induced a hypernormal blood-sugar response, i.e., when absorption was so good that the liver defect could be shown up.

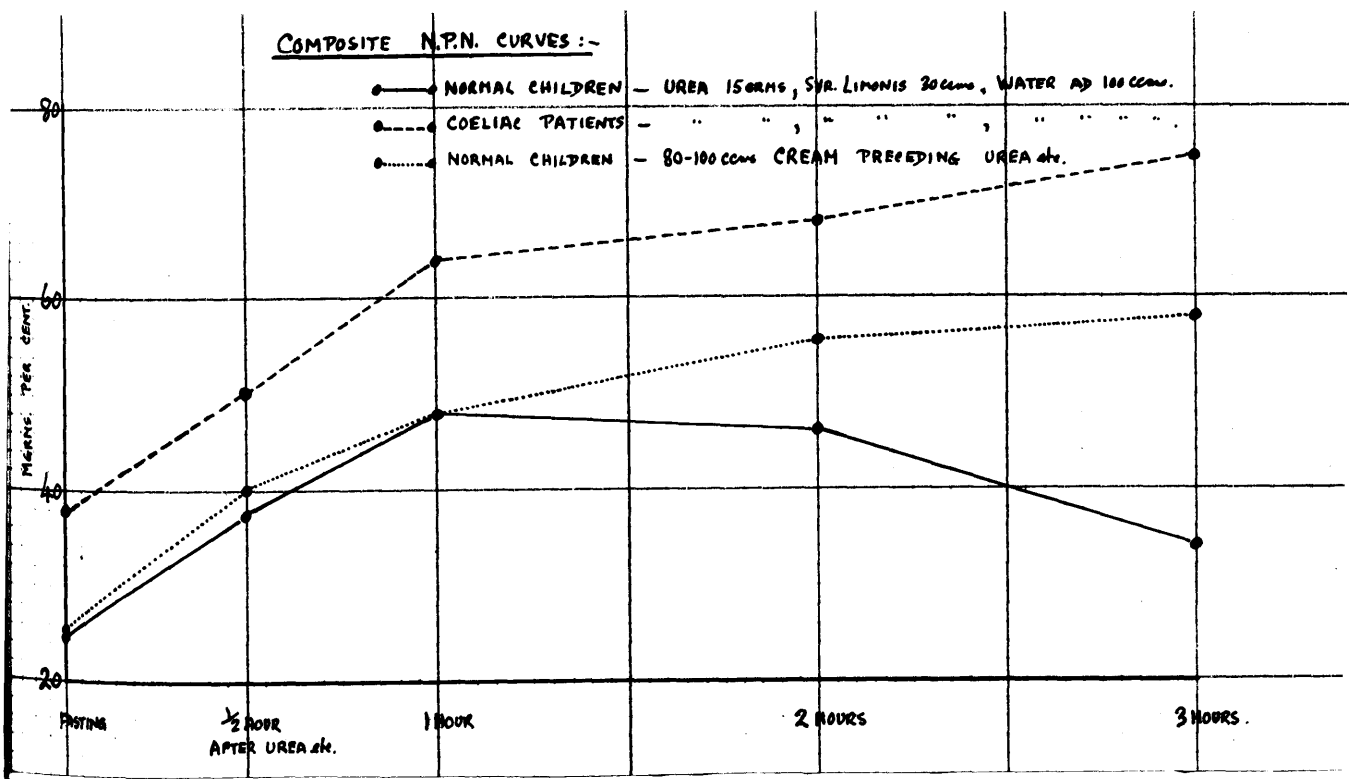


Figure X.

(2) Effect of Fat on the Utilisation of Urea in Normal Children.

In view of the fact that fat was found to hinder absorption of glucose in normal children, it was decided to try its effect on urea utilisation. N.P.N. curves with urea alone were carried out in five normal children, 4 to 11 years, and the results compared with those obtained after ingestion of 80-100 c.cm. 40 per cent. cream immediately preceding 15 grm. urea in 100 c.cm. water with 30 c.cm. syrup of lemon. The results are tabulated below and shown graphically in Figure X.

Table XVI.

No.	Diagnosis.	Age (yrs.)	N.P.N. CURVE (UREA ALONE). Mgrm. %					N.P.N.CURVE (UREA + FAT). mgrm. %				
			Fasting.	½ hr.	1 hr.	2 hrs.	3 hrs.	Fasting.	½ hr.	1 hr.	2hrs.	3hrs.
1.	Convalescent Nephritis.	7	34.2	45.4	50.0	41.6	38.4	27.5	49.5	61.7	63.3	62.5
2.	Convalescent Nephritis.	9	20.0	31.2	43.1	40.0	33.3	28.4	43.8	52.1	53.1	58.8
3.	Convalescent Nephritis.	11	22.3	28.7	57.4	37.3	-	23.1	40.9	45.4	58.5	48.4
4.	Enuresis.	4	21.6	34.2	37.6	48.0	26.1	26.1	29.4	39.6	51.0	60.2
5.	Convalescent Rheumatism.	7	28.5	48.5	55.5	67.5	40.3	25.7	37.1	44.2	52.1	61.7
MEAN:			25.3	37.6	48.7	46.9	34.5	26.2	40.1	48.6	55.6	58.3

The three nephritic cases had normal urea concentration tests as estimated at the same times as the N.P.N. curves. Fasting levels, 20-34.2 mgrm. per cent., compared favourably with those reported by Tindal[94] and the curve in normal children with urea alone closely resembled her average curve. The effect of cream was to produce a curve which followed the normal up to one hour after urea ingestion then continued to rise on an exact parallel with the curve in coeliac disease with urea alone. The average height of rise in the N.P.N. curve of the coeliac as compared with that in the normal with urea and fat was 37.1 mgrm. per cent. as against 32.1 mgrm. per cent., whereas in the normal with urea alone the rise was 23.4 mgrm. per cent. There was no indication of delay in absorption when urea was ingested simultaneously with cream, and no alteration in the urea concentration powers of the kidney was noted in Case 1. Hence the most likely explanation is that the presence of fat in the upper reaches of the intestine produces a transient effect on hepatic function.

SUMMARY OF FINDINGS IN SECTION IV.

(1) There is no impairment of absorption nor excretion of a simple nitrogenous compound such as urea.

(2) Slightly higher fasting N.P.N. values than normal are common to hepatic disease and coeliac disease.

(3) A prolonged high rise in N.P.N. is typical of coeliac disease and hepatic disease when urea alone is ingested and also of normal children when urea and fat are ingested simultaneously.

Conclusion. The evidence is in favour of a liver defect in coeliac disease, which originates from the primary fat disturbance.

V. THE RÔLE OF THE ANTERIOR LOBE OF THE PITUITARY IN COELIAC DISEASE.

The intangible nature of the causative factor in coeliac disease has induced several authors to suggest an endocrine basis, but owing to the difficulty of obtaining positive evidence they have been unsuccessful in convincing other observers.

It has been chiefly the arrest in growth and the disturbance in carbohydrate metabolism which have directed their attention in this direction. As far back as 1908 Herter mentioned the possibility of pituitary insufficiency. Four years later, as mentioned in Section I of this thesis, Ostheimer showed a case at the Philadelphia Pediatric Society and remarked on the fact that treatment with thyroid extract for three months was of no avail but one month's administration of pituitary extract had caused a gain in weight of two pounds. Still[87] (1918) was alive to the possibility of deficiency in the internal secretions and tried thyroid in three cases without success; no improvement in height nor general condition occurred. The administration of a polyglandular extract to another case, however, was followed by an increase of height of $\frac{3}{8}$ inch in 14 days and another $\frac{1}{4}$ inch in the next 12 weeks, but he added that the child at the same time had improved so much as regards general health/

health that she was able to take ordinary diet. He rather favoured a general interference with nutrition as the cause of lack of growth but was willing to accept the view that the internal secretions related to growth regulation might be secondarily involved. Schick and Wagner[82] (1923) found in one case post mortem some changes in the pancreas, thyroid, suprarenals and thymus and on the basis of their findings stipulated a pluriglandular insufficiency in coeliac disease. Subsequent autopsies, however, have not revealed any such abnormalities. A case of coeliac disease with glycosuria led Poynton and Cole[74] (1925) to regard diabetes as a possible accompaniment, owing to the withdrawal of fats from the diet throwing a greater strain on the carbohydrate regulating mechanism already damaged by toxic action. As the complication has not been noted by other observers it may be dismissed as a case of true diabetes in coeliac disease or, as MacRae and Morris suggest, a possible low renal threshold.

In a series of twenty-five cases of coeliac disease, Sauer[79] (1927) found two with an associated hypothyroidism; this fact may or may not be of significance but it is worthy of mention at this stage. MacLean and Sullivan[48] (1929) judging from the clinical picture of coeliac disease and the increased tolerance for dextrose, suggested a similarity to Addison's disease. Asthenia, lack of muscle tone, emotional instability, capricious appetite, gastro-intestinal/

gastro-intestinal upset and bronzing of the skin in severe cases were common to both maladies. This pigmentation of the skin has been noted by other investigators including Thaysen and Svensgaard. Thaysen,[91] and Thaysen and Norgaard[92] (1929) favoured a toxic effect on the endocrine glands as being an explanation of the low blood-sugar curve, the hypernormal rise with adrenalin and the occurrence of tetany, low blood pressure and abnormal pigmentation of the skin. They argued that chronic inanition caused loss of weight and changes in the endocrine glands with the exception of the pancreas. Linder and Harris[46] (1930) attributed the tetany manifestations to hypoparathyroidism. Svensgaard[90] (1931) stressed the inability of coeliac patients to utilise fat and concluded that it did not seem unreasonable to think of a hormone insufficiency and to see a parallel with diabetes mellitus.

The endocrine theories, however, did not meet with the approval of Parsons (1932) who, after quoting some deprecatory remarks on the subject by Morse, made the amusing statement that there was "nothing more to be said or done except perhaps for its followers to drop a few silent tears of regret on the dead body of the endocrine theory." Yet he it was who recorded the fact that for a few years after cure was complete the distribution of fat was very similar to that seen in mild examples of Fröhlich's syndrome. Also/

Also, he described a case of coeliac disease in a girl of 17 years who was markedly dwarfed and showed no signs of secondary sex characteristics. Absence or poor development of primary and secondary sex characters was also noted by Bennett, Hunter and Vaughan in some of their adolescent cases though these authors did not entertain the theory of endocrine dysfunction.

As recently as 1933, Segers[84] has presented an interesting publication, entitled 'Celiac disease; the possible rôle of pituitary insufficiency.' His statements are hypothetical for the most part but he seems impressed by the fact that in coeliac disease, growth, skeletal development and the metabolism of fats and carbohydrates are defective - factors intimately concerned with pituitary function.

Recent years have witnessed a great advance in the elucidation and sorting out of the various hormones of the anterior lobe of the pituitary gland and it was the intimate association of this gland with growth, sex, and the regulation of fat and carbohydrate metabolism which prompted the following investigations in coeliac disease. A few preliminary remarks on the present situation regarding this gland are essential before going on to describe the investigations in coeliac disease.

The Anterior Lobe of the Pituitary.

Evans[12] (1933) has described and given evidence for the existence of seven hormones of the anterior pituitary lobe:-

1. The growth hormone, which has been identified with the eosinophilic cells.
2. The sex or gonadotropic hormones, Prolan A and Prolan B, which may or may not be products of the basophilic cells.
3. The thyrotropic hormone.
4. The lactogenic hormone.
5. The diabetogenic hormone.
6. The adrenalotropic hormone.
7. The fat metabolism hormone.

The growth and sex hormones he accepted without question; the evidence in favour of the thyrotropic and lactogenic hormones was conclusive, but for the last three extremely suggestive. An extensive series of researches on animals by Lücke and his co-workers[47] (1933) has been the means of establishing the significance of certain of these hormones. He demonstrated the acceleration of growth of young dogs, guinea-pigs, rabbits and rats by administration of anterior pituitary preparations orally or intramuscularly. In support of a diabetogenic hormone or, as he preferred to term it, a contra-insular hormone, he showed that removal of the anterior lobe in dogs lowered

the/

the blood sugar by 20-40 per cent. and intensified the hypoglycaemia induced by insulin. Injection of präphyson, a preparation devoid of gonadotropic hormone, in these animals and in normal rabbits, dogs and man raised the blood-sugar and weakened the action of insulin. During pregnancy when the sex hormones are increased there was no evidence of disturbance in carbohydrate metabolism. Hence Lücke concluded that the contra-insular hormone was distinct from the sex hormones. The hyperglycaemic response and the lessened action of insulin was even more marked when präphyson was injected into depancreatised dogs. Thus the contra-insular hormone was identical with the pituitary substance which Houssay and Biasotti[39] (1932-33) found to cause aggravation of diabetes in depancreatised dogs. It differed from the thyrotropic hormone as the latter failed to cause hyperglycaemia and because it was not found essential to have an intact thyroid gland. In view of the fact that it was not ultra-filtrable, Lücke concluded that the contra-insular hormone was also distinct from the fat metabolism hormone. On the other hand it was shown to be a close ally of the growth hormone, perhaps another property of its substance, as preparations containing the growth hormone showed similar actions to those of the contra-insular hormone. The effect of adrenalectomy, denervation of the adrenals, and sympathetic poisons was to prevent the hyperglycaemia/

hyperglycaemia of the contra-insular hormone. Also intramuscular injections of the hormone in normal dogs led to a high concentration of it in the cerebro-spinal fluid. Lücke therefore concluded that this hormone of the anterior lobe found its way into the cerebro-spinal fluid, acted on the sugar centre and thence through the sympathetic and adrenals on the blood-sugar.

This antagonism of the anterior pituitary gland and the pancreas has been recognised for some years past though the real significance of it has only now come to light. Cushing and Davidoff[11] (1927) and Ulrich[95] (1928) were aware that insulin was less effective in the glycosuria of acromegaly than in pancreatic diabetes. Olmstead and Logan[68] (1923) demonstrated severe insulin reactions with hypoglycaemia and convulsions when the hypophysis was removed with the cerebrum in cats. Also, Houssay and Magenta[38] (1925) found in dogs that after the establishment of hypopituitarism by hypophysectomy, hypoglycaemia was more readily induced by insulin injection than in normal dogs.

(1) EFFECT OF INSULIN ON BLOOD SUGAR OF (a) NORMAL and (b) COELIAC SUBJECTS.

(a) Seven children of ages ranging from three to nine years and convalescing from pneumonia, nephritis, etc., were prepared as for a glucose curve and after the fasting blood/

blood specimen was withdrawn in each case 4 units insulin were injected hypodermically. Further specimens of blood were withdrawn at 10 minutes, ½ hour, 1 hour, 1½ hours and 2 hours after the injection. The lowest level of the blood-sugar reached was 51.7 mgrm. per cent. and in no case were hypoglycaemic signs observed. In four of the seven patients the lowest figure was obtained at 1 hour after injection; in the remaining three at 10 minutes to ½ hour after insulin. These findings are in accordance with those of Gilchrist[24] (1932).

Table XVII.

NORMAL CASES.

Case	Age (yrs)	Diagnosis.	Diet.	Units Insulin.	BLOOD SUGAR - Mgrm. per cent.						% Drop
					Fasting.	10 mins. after Insulin.	½ hr.	1 hr.	1½hrs.	2hrs.	
1.	4	Secondary Anaemia.	Light.	4	80.0	76.0	74.3	73.3	74.0	74.6	8
2.	7	Convalescent Rheumatism.	Ordinary	4	76.0	71.4	64.5	54.2	58.8	63.5	28
3.	4	Convalescent Nephritis.	Light.	4	85.1	80.0	71.4	70.0	74.0	?	17
4.	9	Convalescent Chorea.	Ordinary.	4	80.0	51.7	66.7	67.2	70.4	62.7	35
5.	4½	Convalescent Pneumonia.	Ordinary.	4	76.9	54.7	57.7	67.2	60.2	69.7	28
6.	3	Chronic Appendicitis	Ordinary.	4	83.3	80.0	56.8	69.7	67.2	65.2	31
7.	3	Convalescent Chorea.	Ordinary	4	81.6	75.1	62.5	52.6	58.8	58.1	35
MEAN:					80.4	69.8	64.8	64.9	66.2	65.6	19.4

(b) Nine insulin curves were performed on seven coeliac patients and the remarkable difference from the results in normal children was the extremely low sugar level reached in certain cases. Case P.S. gave the phenomenal figure of 14.0 mgrm. per cent. and it was thought that some error in estimation or technique had occurred, but on repeating the experiment four days later an exactly similar curve was obtained, the low figure of 15.1 mgrm. per cent. being returned. Values as low as these have occasionally been reported in the literature (cf. Meulengracht, Acta med. Scand., 1928, Suppl. 26, 181: 10 mgrm. per cent.) but most authors hold that such a low blood-sugar is incompatible with life. Yet Case P.S. did not present any more severe hypoglycaemic signs than the others in the series. In all but case G.B., who presented the least response to insulin as regards diminution in blood-sugar, mild hypoglycaemic signs were noted within 10 minutes to 1 hour after insulin injection. These took the form of pallor, drowsiness, perspiration, thirst, rapid pulse and irritability when the child was roused. Convulsive attacks were not produced in any of the patients.

In all cases the initial drop within the first 10 minutes was more precipitous than in the normal subjects and thereafter the curve continued to drop gradually and showed little or no tendency to revert to normal at the end

of/

Table XVIII.

COELIAC PATIENTS.

Case.	Age (yrs)	Date.	Diet.	Insulin Dose. (Units)	BLOOD SUGAR - Mgrm. per cent.						% Drop.
					Fasting.	10 mins. after Insulin.	½ hr.	1 hr.	1½ hrs.	2 hrs.	
G.B.	4	1/5/33	Milk + Sugar.	4	66.7	52.2	58.3	53.5	48.4	59.0	27
B.G.	3	15/9/33	Butter-Curd Mixture.	4	60.0	40.8	41.6	33.3	32.3	29.8	50
W.McK.	2½	17/6/33	Milk.	4	62.5	37.0	36.4	36.1	34.9	35.7	44
D.McL.	3 4/12	29/5/33	Curd Mixture. Curds. Bananas.	4	56.1	42.3	39.4	37.0	27.5	34.8	50
		2/6/33	"	4	59.3	44.6	25.0	25.0	26.3	32.2	57
M.O'B.	2½	21/6/33	Sweet Curd Mixture. Curds. Bananas.	4	63.8	45.5	37.0	39.2	33.3	33.3	48
P.S.	2 9/12	29/5/33	Skim Milk. Bananas.	3	38.5	21.7	20.8	19.4	14.0	14.3	63
		2/6/33	"	3	38.4	15.1	17.8	16.1	16.1	20.0	60
I.W.	2 9/12	31/5/33	Skim Milk. Curds. Bananas.	4	60.6	52.6	37.0	40.0	44.4	47.6	37
MEAN:					56.2	39.1	34.8	33.3	30.8	34.1	45.2

of 2 hours. The average drop in mgrm. per cent. of the blood-sugar in the normal subject was 15.6 as against 25.4 in the coeliac patient, but owing to the lower fasting sugar value in coeliac disease the percentage drop showed a greater difference, viz., 19.4 as against 45.2 In other words there is a more/

more pronounced reaction to insulin injection in the coeliac patient. This is readily seen in Figure XI.

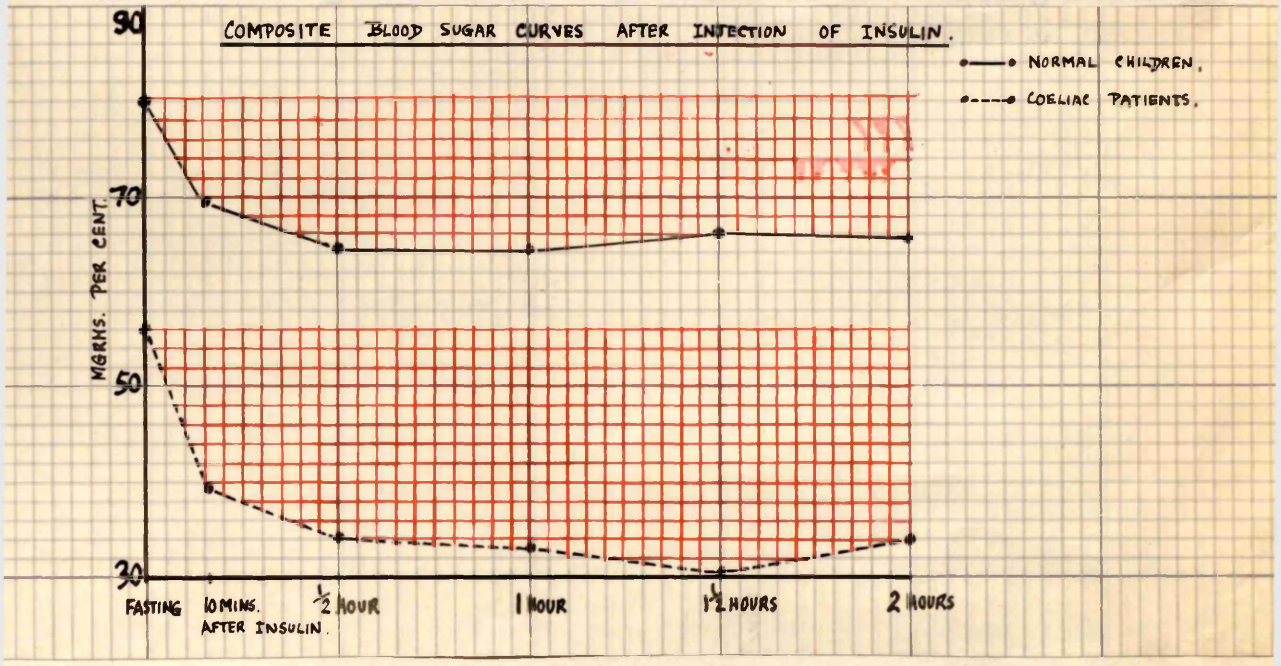


Figure XI.

Of more than passing interest is the fact that Gilchrist (24) found identical curves with insulin in her normal cases on a high fat diet.

(2) EFFECT OF ANTERIOR PITUITARY LOBE EXTRACT ON BLOOD-SUGAR CURVE IN COELIAC DISEASE.

For this investigation and throughout subsequent experiments Armour's anterior lobe extract was employed, and for purposes of convenience it will be referred to as 'antuitrin.'

The hypodermic injection of 1 c.cm. of antuitrin in/

in one case (G.B.) of coeliac disease on two nights prior to the withdrawal of the morning fasting specimen of blood for sugar estimation produced an interesting result. This child had never shown a higher fasting sugar level than 66.7 mgrm. per cent. in previous experiments but after the antuitrin injections a normal blood sugar was obtained, viz., 83.7 mgrm. per cent. Injection of a further 1 c.cm. immediately after removal of the fasting blood specimen was followed by little or no change in the sugar level at 10 minutes, ½ hour, 1 hour, 1½ hours and 2 hours afterwards. The results pointed to a remote rather than an immediate effect of antuitrin and it was decided to give antuitrin 1 c.cm. on two nights prior to the carrying out of an ordinary glucose curve (1 grm. per kilo). In contrast to the comparatively flat curve obtained in this patient previous to the experiments with antuitrin a perfectly normal curve with a normal fasting level was found. The coeliac condition in this case had not improved at the time of the second glucose curve; in fact, he had been suffering from diarrhoea for 4 days. Hence it is hardly likely that the normal curve was due to the stage of convalescence reached.

In all, eight such experiments have been performed in six coeliac patients (see Table XIX, Figure XII). Each case showed some heightening of the curve, the extent of rise/

Case.	Age (yrs.)	Da
G.B.	8 4 12	8/4/
	4 9/12	20/5/
B.G.	3 2/12	11/9/
	3 3/12	13/1(
W.McK.	2 6/12	7/6/
		5/7/
	2 9/12	29/9/
		16/1(
D.McL.	3 7/12	7/6/
		10/6/
M.O'B.	2 6/12	19/6/
		5/7/
	2 10/12	9/10/
		10/11/
P.S.	2 10/12	22/6/
		24/6/

Table XIX.

Case.	Age (yrs.)	Date.	Diet.	Condition.	Glucose or Antuitrin + Glucose.	BLOOD SUGAR - Mgrm. per cent. Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm.%
G.B.	4 8/12	8/4/33	Ordinary.	Good.	Glucose (1 grm./k.)	66.7	111.1	83.3	80.6	67.9	44.4
	4 9/12	20/5/33	Light.	Good (but Diarrhoea +)	Glucose preceded by Antuitrin.	86.0	121.9	140.8	70.1	69.4	54.8
B.G.	3 2/12	11/9/33	(Skim Milk (Curds (Bananas.	Moderate.	Glucose alone.	60.0	62.5	79.7	104.8	88.9	44.8
	3 3/12	13/10/33	"	"	Antuitrin + Glucose.	70.1	111.1	100.5	85.1	69.1	41.0
W.McK.	2 6/12	7/6/33	Light.	Moderate.	Glucose alone.	58.0	66.7	64.1	63.0	60.0	8.7
		5/7/33	Milk.	"	Antuitrin + Glucose.	71.4	87.7	93.9	100.0	71.4	28.6
	2 9/12	29/9/33	(Skim Milk (Curds (Bananas.	Good.	Glucose alone.	64.5	76.9	101.7	99.0	84.0	37.2
		16/10/33	"	"	Glucose preceded by Antuitrin.	71.4	84.0	117.6	115.6	115.6	46.2
D.McL.	3 7/12	7/6/33	(Curd Mixture (Curds (Bananas.	Very good.	Glucose alone.	56.6	71.4	76.9	60.2	61.2	20.3
		10/6/33	"	"	Antuitrin + Glucose.	74.0	133.3	102.5	64.5	76.9	59.3
M.O'B.	2 6/12	19/6/33	(Curd Mixture (Curds (Bananas.	Good.	Glucose alone.	62.5	88.2	79.7	100.0	62.5	37.5
		5/7/33	"	"	Antuitrin + Glucose.	76.9	100.0	125.0	111.1	80.0	48.1
	2 10/12	9/10/33	(Skim Milk (Curds (Cornflakes (Bananas.	Very good.	Glucose alone.	64.5	100.0	85.1	86.9	74.0	35.5
		10/11/33	"	"	Antuitrin + Glucose.	76.9	133.3	108.1	109.2	70.6	56.4
P.S.	2 10/12	22/6/33	Skim Milk.	Very poor.	Glucose alone.	50.0	60.0	65.2	54.5	43.5	15.2
		24/6/33	"	"	Antuitrin + Glucose.	50.0	68.5	85.7	100.0	85.7	50.0
			MEAN:		Glucose alone	60.4	79.6	79.5	81.1	67.8	20.7
			MEAN:		Antuitrin + Glucose.	72.1	105.0	109.3	94.5	79.8	37.2

BLOOD SUGAR CURVES OF COELIAC PATIENTS BEFORE AND AFTER ANTUITRIN TREATMENT.

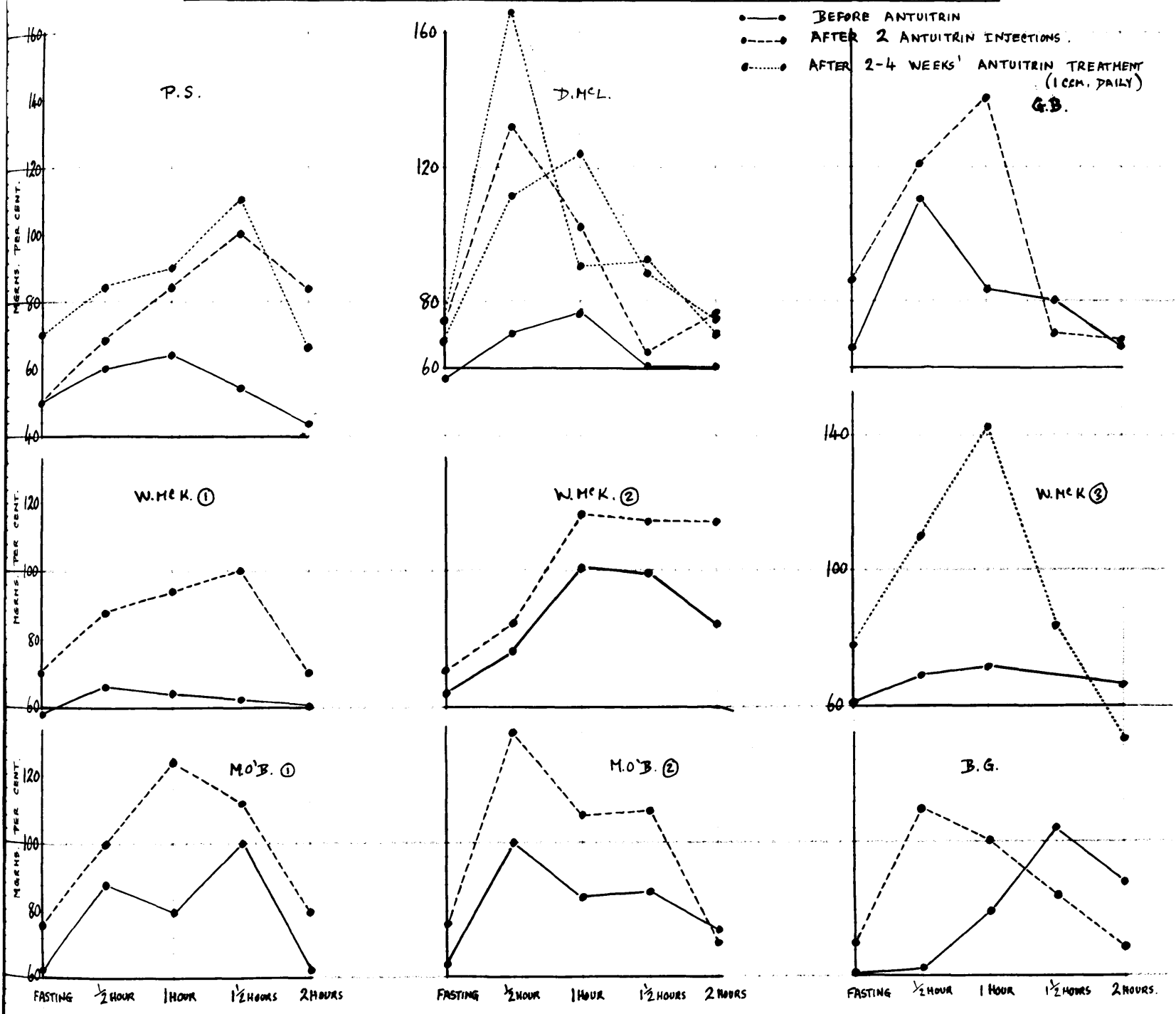


Figure XII.

rise being less striking in those showing the most severe coeliac condition. Only one patient (P.S.) presented no rise in the fasting sugar level; she was in an emaciated state, being only 50 per cent. of her expected weight. As will be seen later, however, the fasting level rose after three weeks' antuitrin treatment.

Three of the patients were treated with antuitrin 1 c.cm. daily for a period of two to four weeks and blood-sugar curves at the end of this time presented the following features. Fasting levels which had not risen or only slightly risen with two doses antuitrin showed a definite approach towards normal values with prolonged antuitrin administration. (See Table XX, Figures XII and XIII).

Table XX.

Case.	Date.	Diet.	Condition.	Duration of Antuitrin Treatment.	BLOOD SUGAR - Mgrm. per cent. Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mgrm.%
I.McK.	8/3/34	(Skim Milk (Curds	Poor.	Before.	61.7	69.0	71.4	-	66.7	9.7
	20/3/34	"	"	After 2 wks	78.4	111.1	142.8	83.3	50.0	64.4
D.McL.	7/6/33	(Curd Mixture.Curds. (Bananas.	Good.	Before.	56.6	71.4	76.9	60.2	61.2	20.3
	5/7/33	"	"	After 3 wks	69.0	111.1	125.0	89.7	74.0	56.0
	13/7/33	"	"	After 4 wks	74.1	166.7	90.9	93.9	70.1	92.6
P.S.	22/6/33	(Skim Milk.	Very poor.	Before.	50.0	60.0	65.2	54.5	43.5	15.2
	13/7/33	"	"	After 3 wks	70.1	85.1	90.9	111.1	66.7	41.0
		MEAN:		Before	59.4	66.8	71.2	57.4	57.1	11.8
		MEAN:		After 2-4 weeks Antuitrin.	72.9	118.5	112.4	94.5	65.2	45.6

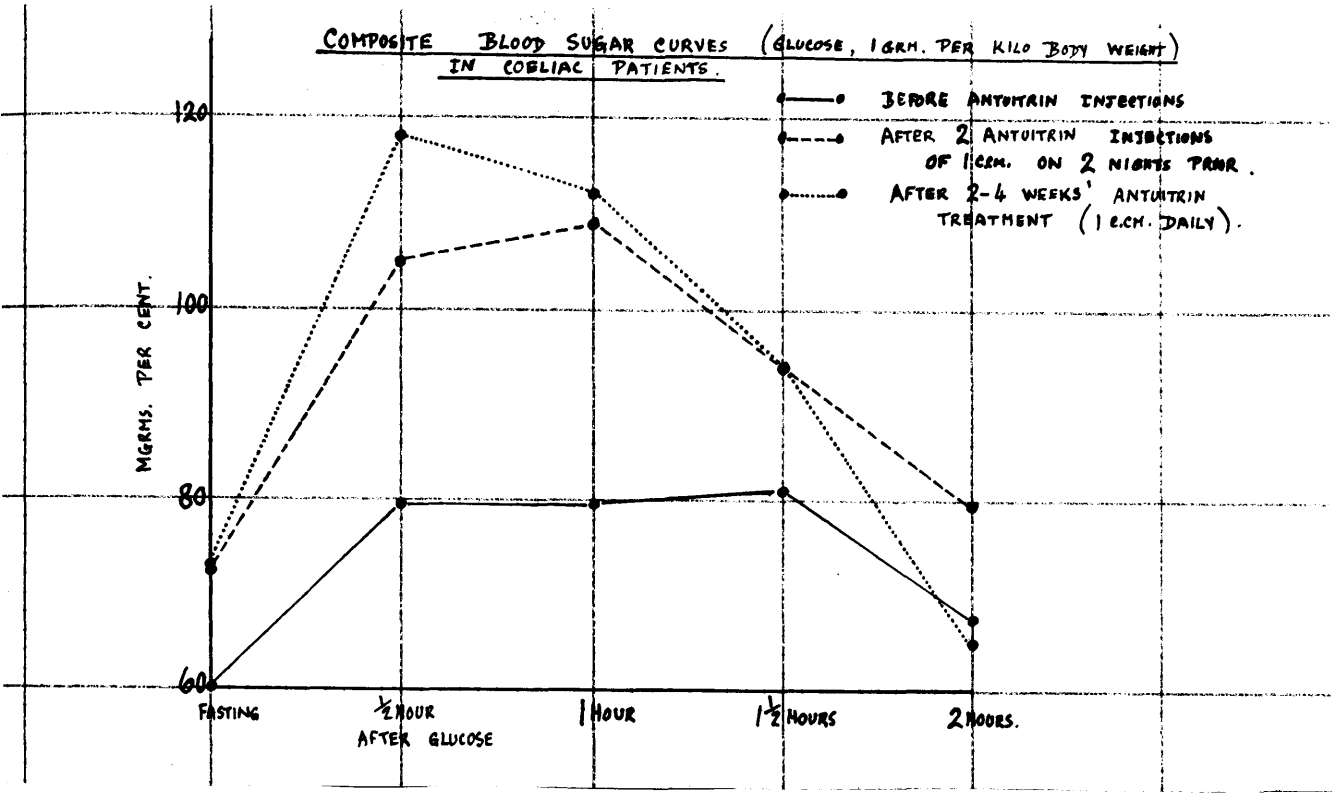


Figure XIII.

In two cases the maximum sugar level reached was hyper-normal, being 142.8 mgrm. per cent. and 166.7 mgrm. per cent. Except in the case of P.S. the maximum level occurred within ½ to 1 hour after glucose ingestion. This exhibited a return to the normal contour of sugar curve. When the composite curve was compared with the average glucose curve in normal children of the same age-group (see Figure III and Table IV) it was found that the two corresponded. It would appear then that antuitrin is capable of producing a normal sugar curve in coeliac disease.

(3) EFFECT OF ANTUITRIN ON SUGAR CURVE IN NORMAL SUBJECTS.

Two children of ages 6 and 7 years convalescing from pneumonia and nephritis respectively were given injections of antuitrin 1 c.cm. on two nights prior to blood-sugar curves being done and the results compared with the curves obtained before the antuitrin was given, i.e., the same experiment was carried out as in the coeliac patients. There was no rise in the fasting nor maximum levels of the blood-sugar curves with antuitrin. The only difference noted was in the contour of the curves, the peak being shifted to the left. This acceleration to the maximum coincided with the finding in coeliac cases.

Table XXI.

Case	Date	Amount Glucose, Antuitrin, &c.	BLOOD SUGAR CURVE - Mgrm. per cent.					Rise in mgrm.%.
			Fasting.	½ hr.	1 hr.	1½ hrs.	2 hrs.	
1	22/1/34	Glucose 1 grm./kilo.	76.9	139.8	151.5	111.1	68.9	74.6
	24/1/34	Glucose 1 grm./kilo preceded by Antuitrin.	78.1	145.9	142.8	72.7	66.7	67.8
2	22/1/34	Glucose 1 grm./kilo.	80.0	91.3	138.8	126.6	83.3	58.8
	24/1/34	Glucose 1 grm./kilo preceded by Antuitrin	80.3	136.0	133.3	80.0	62.5	56.0
MEAN:		GLUCOSE CURVE BEFORE	78.4	115.5	145.1	118.8	76.1	66.7
		" " AFTER ANTUITRIN	79.2	140.9	138.1	76.3	64.6	61.7

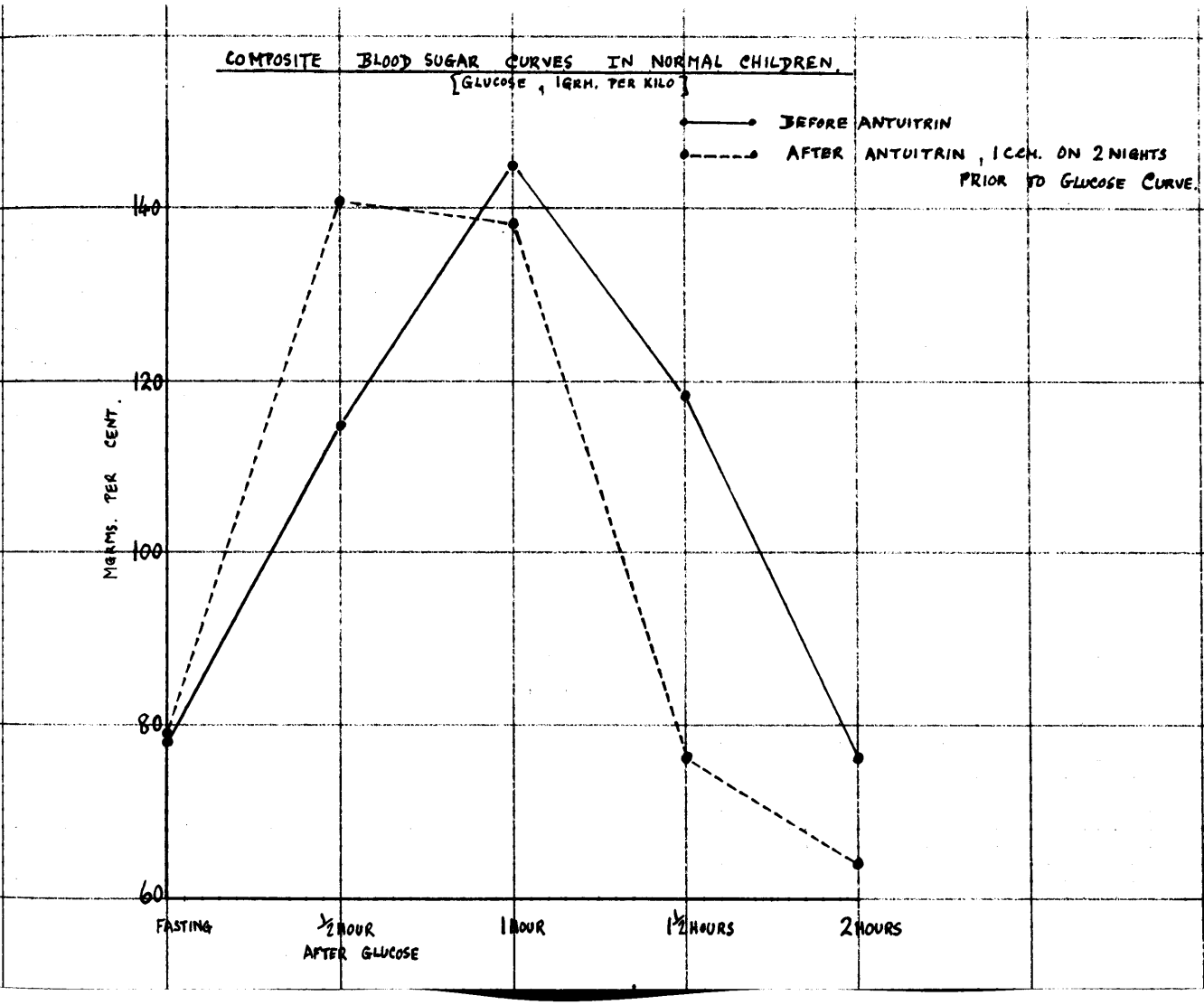


Figure XIV.

(4) DOES ANTUITRIN ALTER THE N.P.N. CURVE IN COELIAC DISEASE?

That the anterior lobe of the pituitary has some relation to protein metabolism as well as that of carbohydrates and fats has been considered by several investigators. Fulton and Cushing[20] (1932) found in patients with/

with hypopituitarism a delayed though normal specific dynamic action of protein. Again, Gaebler[21] (1933) caused a marked fall in the excretion of urea and a decrease of blood N.P.N. by injection of alkaline extracts of anterior pituitary for one to two days into adult female dogs. He regarded the result as due to an increased retention of nitrogen.

On the strength of positive results with antuitrin on sugar curves in coeliac disease it was decided to try out its effect on the abnormal N.P.N. curve. Two coeliac patients were given injections of antuitrin 1 c.cm. on three nights prior to the carrying out of the usual N.P.N. curve and the results compared with the curves obtained in the same cases before the experiment. Though the curves after antuitrin showed slightly lower values at two and three hours after urea ingestion these were well above the fasting level. Also there was no sign of lowering of the fasting value - in fact, in one case a much higher figure was obtained. In other words, antuitrin did not produce normal N.P.N. curves in these two cases.

Table XXII.

Case.	Age (yrs.)	Diet.	Date.	Amt.Urea, &c.	N.P.N. CURVE - Mgrm. per cent.				
					Fasting.	½ hr.	1 hr.	2 hrs.	3 hrs.
M.O'B.	2½	Coeliac.	24/6/33	Urea 15 grm.	38.4	62.5	96.1	90.9	83.3
		"	6/7/33	Urea 15 grm. preceded by Antuitrin.	30.8	50.0	54.3	67.5	64.1
W.McK.	2½	Light. Ordinary.	14/6/33	Urea 15 grm.	34.7	55.5	66.6	73.5	78.1
		Milk (whole).	6/7/33	Urea 15 grm. preceded by Antuitrin.	54.3	55.5	71.4	67.5	64.1

(5) EFFECT OF ANTUITRIN ON FAT METABOLISM OF THE COELIAC PATIENT.

The mode of action of the fat metabolism hormone of the anterior lobe of the pituitary is still so imperfectly understood and results of experiments on blood fats in animals have been so conflicting that no attempt will be made here to summarise previous findings. Suffice it to say that there is a hormone of the anterior lobe which is concerned with fat metabolism and which, as observed by Magistris[52] (1933) is present in the blood especially after fatty meals and during the ketosis of starvation.

Three coeliac patients were given daily injections of antuitrin 1 c.cm. for a period of two to three weeks and thereafter the faeces were collected over a period of six to seven days. The antuitrin treatment was continued during the time they were 'on metabolism;' the diet was a measured one sufficient for caloric requirements and was kept the same throughout the investigation, aliquot specimens being reserved daily for estimation of the fat intake. In each case the fat metabolism had been estimated over six to seven days just prior to the commencement of antuitrin treatment so that results were strictly comparable.

In one of the cases (H.B.) a further metabolism estimation was made at a later date after six weeks' treatment with antuitrin.

Table XXIII.

Case.	Age (yrs)	Diet.	Before or After Antuitrin.	Dates.	Daily Dried Faeces (grm.)	Total Fat %	Neutral Fat %	Free Fatty Acids %	Comb. Fatty Acids %	Daily Fat Intake (grm.)	Daily Fat Output (grm.)	Fat Absorption (per cent.)
P.S.	2 10/12	2% Milk. 1500 c.cm.	Before.	13-20/6/33	11.62	35.41	5.47	16.75	13.19	27.44	4.200	84.7
		"	After 2 wks. Antuitrin.	5-12/7/33 (Ant.contd.)	8.22	24.16	3.82	16.62	4.54	29.82	1.987	93.3
W.McK.	3 3/12	2% Milk. 1800 c.cm.	Before.	1-7/3/34	45.50	56.38	5.16	40.73	10.49	70.45	25.643	63.6
		Curds 210 grm.	After 2 wks. Antuitrin.	21-27/3/34 (Ant.contd.)	28.60	40.49	4.71	29.40	6.38	70.04	11.593	83.4
H.B.	4½	Whole Milk Egg Yolk	Before.	1-7/3/34	18.30	27.31	3.49	7.71	16.11	25.90	5.008	80.7
		"	After 2 wks. Antuitrin.	21-27/3/34 (Ant.contd.)	18.60	17.50	4.10	9.67	3.73	25.40	3.250	87.2
		Milk 1260 c.cm. Bread 3 oz. 2 Bananas. Mince. Jelly. Rye Vitas. Orange Juice.	After 6 wks. Antuitrin.	28/5/34-4/6/34 (Ant.contd.)	18.54	26.70	2.56	6.73	17.40	44.86	4.951	88.9

It will be observed that higher fat absorption figures were obtained in all three children after antuitrin injections. With reference to W. McK. there was the remarkable rise of 20 per cent.: the daily weight of dried faeces fell from the high figure of 45.5 grm. to 28.6 grm. Even more striking was the fact that the dried ground faeces after antuitrin were noticeably freer from fats and of a much more powdery consistency than before antuitrin administration.

P.S. was absorbing as much as 93.3 per cent. of the fat intake after antuitrin treatment, i.e., fat absorption was almost normal. The daily weight of dried faeces dropped from 11.62 grm. to 8.22 grm., the lowest figure obtained for daily bulk of faeces throughout all the metabolism estimations of the present series of coeliac patients. In the case of H.B. the daily faecal weight did not alter appreciably even after the seven weeks' antuitrin period, but the fat content diminished, the stools becoming more normal in type.

Clinical changes during antuitrin treatment were also in evidence. P.S. who was in very poor condition at the beginning of the experiment succeeded only in maintaining her weight, but W. McK. gained $2\frac{1}{2}$ lbs in the three weeks, while H.B. increased in weight by almost 4 lbs over the seven weeks' antuitrin period. No increase in height was noted in any of the patients.

SUMMARY OF FINDINGS IN SECTION V.

(1) Coeliac patients are hypersensitive to insulin, the blood-sugar falling to an abnormally low level and showing no tendency to revert to normal at the end of two hours. Mild hypoglycaemic signs are frequently present.

Normal children on the other hand show a slight response to insulin, while hypoglycaemic signs are not obtained.

(2) If antuitrin 1 c.cm. be injected hypodermically into a coeliac patient on two successive nights prior to a blood-sugar test the fasting level tends to approach the normal and the curve becomes less flat or of normal height. Daily antuitrin treatment for two to four weeks tends to produce an increasingly higher rise in the curve and to bring the peak over to the left, i.e., with the maximum level in ½ to 1 hour.

In normal subjects no rise in fasting level occurs nor is the curve heightened, but the maximum may occur earlier than without antuitrin.

(3) There is no evidence that antuitrin has any effect on the abnormal N.P.N. curve of coeliac disease.

(4) Fat retention is apparently improved by daily administration of antuitrin to coeliac cases.

DISCUSSION.

The results of the foregoing investigations into the metabolism of fats, carbohydrates and proteins in coeliac disease and the experiments with anterior pituitary lobe extract and insulin point to definite conclusions with an important bearing on the pathogenesis of this symptom complex. Evidence has been brought forward to show that in the coeliac patient

(1) The absorption of fats, carbohydrates and (to a less extent) proteins, is defective.

(2) The intermediate metabolism of carbohydrates and proteins in the liver is faulty, the defect arising from the primary fat disturbance.

(3) The administration of anterior pituitary lobe extract appears to correct the defective metabolism of carbohydrates and fats.

In view of these facts one is justified in concluding that not one but several factors are involved in the coeliac upset. The primary offender however would appear to be the anterior pituitary lobe with its constituent hormones, the lesion being one of hypopituitarism. Deficiency in the particular hormone of the anterior lobe concerned with fat regulation/

regulation deranges fat metabolism. The sluggish absorption of fats in turn defers absorption of carbohydrates (see Section III, D, p. 51.). Secondary liver dysfunction is set up (see Section III, B; IV, (1).); carbohydrates and proteins are incorrectly dealt with and thus a vicious circle is established. Moreover, insufficient contra-insular hormone in the anterior lobe as evidenced by the effect on the flat blood-sugar curve of small doses of antuitrin and the hypersensitiveness of coeliac patients to insulin (see Section V, (1), (2).) further aggravates conditions. As has been previously pointed out the ideal accompaniment for this hormone is an intact adrenalin mechanism and it is doubtful whether in coeliac disease the suprarenals are working efficiently (see later in this discussion).

The improvement obtained biochemically on administration of anterior lobe extract to the present series of patients, the changed character of the stools, and the considerable increase in body weight in two cases favour the postulation of hypopituitarism in coeliac disease.

Clinical data are available to support the theory. The illness frequently dates from an acute infection which might account for a sudden arrest in function of the anterior lobe of the pituitary. This gland has much to do with growth, and dwarfism is an outstanding feature in coeliac disease. The fact that no increase in height was obtained in any of the/

the patients treated with antuitrin does not discourage the theorist as one would require to prolong the treatment for some months before coming to a definite conclusion on this point. Another well-marked feature of coeliac disease is the intolerance to fats and carbohydrates, and the frequency of relapses when these constituents of the diet are introduced prematurely - due no doubt to the lack of fat and carbohydrate regulating hormones. Sometimes these 'crises' occur for no apparent reason and in this respect coeliac disease simulates Simmond's disease (hypopituitarism).

Absence or poor development of primary and secondary sex characters have been already mentioned as an occasional occurrence in adolescent cases of Gee's disease and it is well known that the anterior pituitary lobe furnishes sex hormones.

To continue the theory further one might argue that there is clinical evidence of secondary involvement of other endocrine glands. Lack of adrenalotropic hormone could explain such accompaniments of coeliac disease as hypotonicity of muscles, mental apathy, pigmentation of skin and a tendency to low blood pressure and subnormal pulse rates. In the present series, systolic blood pressures of 60 to 80 mm. Hg. were commonly found, while pulse rates of 80 to 90 per minute were often recorded. Again, deficiency in thyrotropic hormone might account for the thin short scanty/

scanty hair of the coeliac patient and the fact that hypothyroidism occasionally accompanies coeliac disease (cf. Sauer - (79), (1927)).

It might be contended that if coeliac disease originates from hypofunction of the anterior pituitary lobe, changes in the gland post-mortem should be obvious. The literature on the subject reveals no record of such, and no gross lesion was visible in the gland of B.G., the one fatal case of the present series. When one considers how often diabetes mellitus is accompanied by no abnormality of the pancreas, the pituitary theory cannot be discarded on these grounds.

Several of the coeliac patients had an X-ray of skull taken but no shallowing or diminution in the size of the sella turcica could be detected. In spite of these negative findings ample positive evidence has been cited to support a deficiency of anterior pituitary lobe secretion as a feasible etiological factor in coeliac disease.

APPENDIX.

Case Histories of Coeliac Patients

CASE I.

Name: Gerald Baird.

Age: $4^2/12$ years.

Admitted: 22/9/32.

Social Conditions: Poor.

Family History: Mother died of phthisis and diabetes when patient was aged 1 year.
Father has a duodenal ulcer.
3rd child - other two alive and well.

Previous History: Full time normal labour. Healthy at birth. Bottle-fed (cow's milk) till 10 months and throve well apart from chicken-pox at 6 months.
Cut first tooth at 8 months. Started to walk at 10 months.
Whooping-cough at $3^4/12$ years and 'has not been the same child since.'

History of Illness: Recovery from whooping cough was slow - cough persisted and he remained pale and listless.
For 3 months prior to admission he suffered from intermittent diarrhoea with loose offensive stools numbering four or five daily, occasional vomiting, anorexia, cough and listlessness.
In spite of a month's holiday in country he showed no improvement, lost weight, and developed cervical adenitis and a septic finger three days before admission.

Condition on Admission: A pale, somewhat undernourished child - 74 per cent. of his expected weight and 92 per cent. of expected height.
Cervical abscess and septic finger.
Several carious teeth. Muscles flabby.

Abdomen/

CASE I (contd.)

Abdomen: Prominent, tympanitic - no masses palpable. Motions normal in colour and not offensive nor frequent.

Chest: Impaired percussion note over right base behind and deficient breath sounds. X-ray showed extended hilum shadows.

Tuberculin Skin Tests (Pirquet and Mantoux) were positive.

Heart: Sounds of poor quality and pulse-rate slow.

Urine: No abnormality.

Nervous System: No abnormality (knee-jerks present).

Leucocytes: 9,800 per c.mm.

SPECIAL INVESTIGATIONS:

Biochemical Tests: See "G.B." in Sections II-V.

Course of Illness:

22/9/32-7/10/32:	R.H.S.C.	After incision of the cervical abscess and the septic finger the child's general condition improved with milk diet and as he showed no sign of diarrhoea after two weeks' stay a diagnosis of mediastinal tuberculosis was the one favoured.
7/10/32-4/11/32:	R.H.S.C. Country Branch, Drumchapel.	On light diet he remained comparatively well.
4/11/32-4/3/33:	Holiday Home, Saltcoats.	Occasional diarrhoea and persistence of cough.

CASE I (contd.).

4/3/33- 3/4/33:	At home.	On 30/3/33, at age of $4^{8}/12$ years, he reported at R.H.S.C. with a history of recurrence of diarrhoea and it was found that the abdomen was very prominent while the ankles showed some oedema. A diagnosis of coeliac disease was suggested and he was readmitted to R.H.S.C. for investigation.
3/4/33- 4/6/33:	R.H.S.C.	In 6 months he had not grown any in height and was still 78 per cent. of his expected weight. The wrists showed bony enlargement and slight genu valgum was noted. Chest signs were no longer evident. Motions during the next month were bulky, pale, offensive and inclined to be loose and frequent. Thereafter they became more formed and infrequent. Pending the result of the metabolism and owing to the improvement in stools and general condition he was dismissed home on ordinary diet.
21/8/33- 21/9/33:	Saltcoats Convalescent Home.	Motions pale and offensive, one or two daily. Did not gain in weight but grew 1 cm.
21/9/33 onwards:	At home.	He was sent to a special school and reported at R.H.S.C. fortnightly. The stools did not improve with ordinary diet though he showed slight rise in weight and height and in November 1933, a strict coeliac diet was commenced (Skimmed Milk, 2 pints daily; Curds from 1 pint whole milk; 3 bananas; cornflakes; juice of lean meat or fish or rabbit). Radiostol pellets, one twice daily, were also given. Apart from a short time in December 1933, when the father was in hospital and the diet was not adhered to, the child showed slow but steady improvement. The diet was supplemented (skimmed milk, 3 pints daily; curds; 3 bananas; cornflakes/

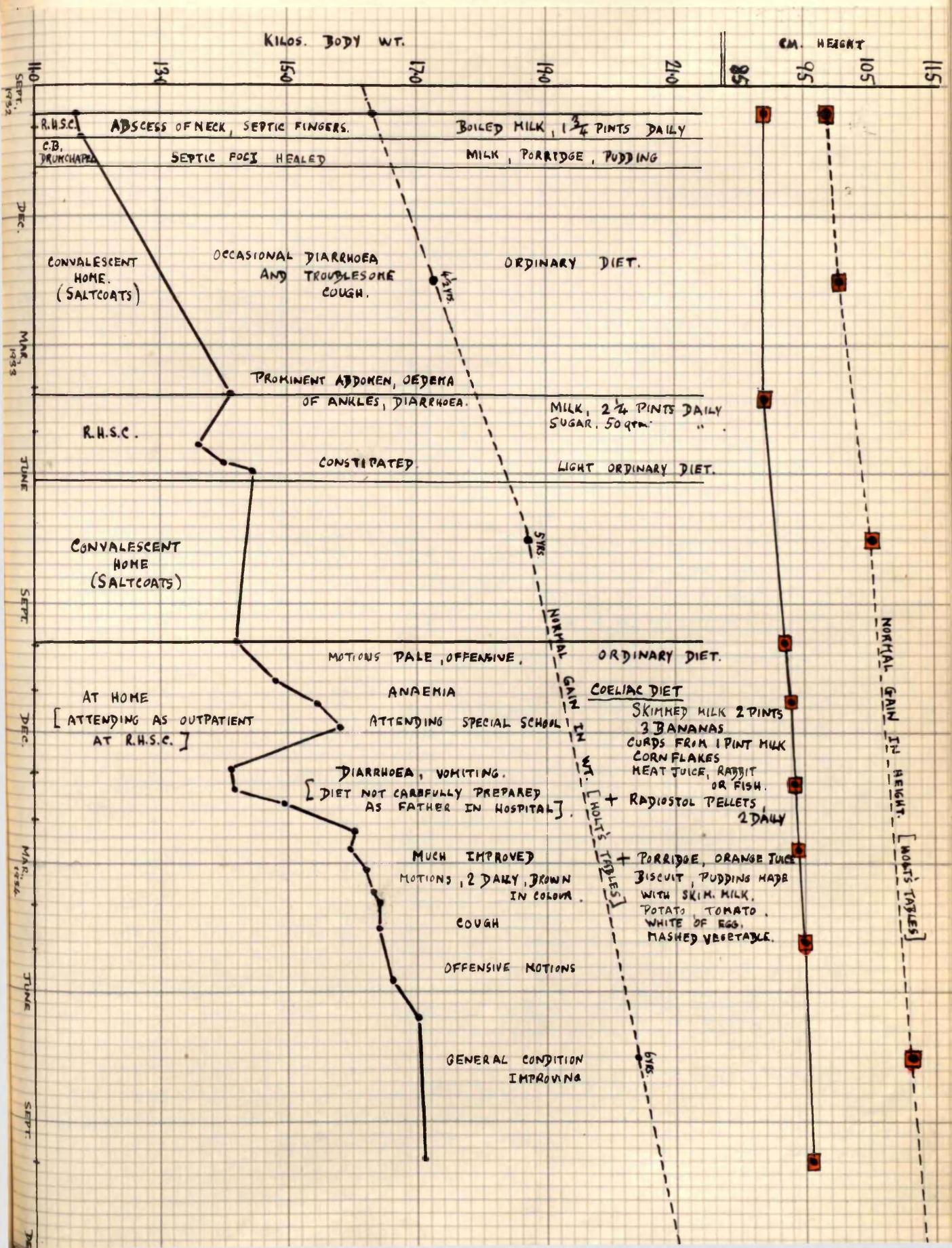
CASE I (contd.).

cornflakes; orange juice; tomatoes; apples; vegetables such as potato, mashed turnip and carrot; puddings made with skimmed milk; biscuits; occasionally brown bread). The motions though still numbering one to two daily became more normal in colour, less offensive and of better consistency. On 28/3/34 he was 86 per cent. of his expected weight but still only 87 per cent. of his expected height. X-ray of wrist at that time showed delayed ossification ($3\frac{1}{2}$ years) but no rickets.

Condition on 25/9/34 (aet. $6^{2}/12$ years).

Child looked well, was lively and appeared to be getting on well at school. He was 82 per cent. of his expected weight and 86 per cent. of his expected height. Diet had not been altered and he was taking it well. Abdomen was still prominent, but motions, one or two daily, were normal in colour and not offensive.

SEE GRAPH - next page.


KILOS. BODY WT.
140
130
120
110
100
90
CM. HEIGHT
85
95
105
115
SEPT. 1952
DEC.
MAR. 1953
JUNE
SEPT.
DEC.
MAR. 1954
JUNE
SEPT.
R.H.S.C.
C.B. DRUMCHAPEL
ABSCESS OF NECK, SEPTIC FINGERS.
SEPTIC FOCI HEALED
BOILED MILK, 1¾ PINTS DAILY
MILK, PORRIDGE, PUDDING
CONVALESCENT HOME. (SALTCOATS)
OCCASIONAL DIARRHOEA AND TROUBLESOME COUGH.
ORDINARY DIET.
4 YRS.
PROMINENT ABDOMEN, OEDEMA OF ANKLES, DIARRHOEA.
MILK, 2¼ PINTS DAILY
SUGAR, 50 grm. " .
R.H.S.C.
CONSTIPATED
LIGHT ORDINARY DIET.
5 YRS.
CONVALESCENT HOME (SALTCOATS)
NORMAL GAIN IN HT. [HOLT'S TABLES]
MOTIONS PALE, OFFENSIVE.
ORDINARY DIET.
AT HOME
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
ANAEMIA
ATTENDING SPECIAL SCHOOL
COELIAC DIET
SKIMMED MILK 2 PINTS
3 BANANAS
CURDS FROM 1 PINT MILK
CORN FLAKES
MEAT JUICE, RABBIT OR FISH.
+ RADIOSTOL PELLETS, 2 DAILY
DIARRHOEA, VOMITING.
[DIET NOT CAREFULLY PREPARED AS FATHER IN HOSPITAL].
NORMAL GAIN IN HT. [HOLT'S TABLES]
MUCH IMPROVED
MOTIONS, 2 DAILY, BROWN IN COLOUR.
+ PORRIDGE, ORANGE JUICE BISCUIT, PUDDING MADE WITH SKIM. MILK, POTATO, TOMATO, WHITE OF EGG, MASHED VEGETABLE.
COUGH
OFFENSIVE MOTIONS
GENERAL CONDITION IMPROVING
5 YRS.

CASE II.

Name: Betty Galbraith.

Age: 13/12 years.

Admitted: 7/8/31.

Social Conditions: Moderately good.

Family History: Father and mother healthy. Another child born in 1932 is alive and well.

Previous History: Full-time normal labour. Apparently healthy at birth (wt. 7 lbs.). Bottle-fed on boiled cow's milk till 11 months and throve well. Did not cut first tooth till 11 months. Began to talk at 1 year, but was not attempting to walk at time of admission.

History of Illness: At 11 months, with onset of dentition, she began to lose appetite (previously voracious), then vomiting and diarrhoea followed. On milk diet, meat juices, whey and albumen water the attack abated in a month, but she remained listless and developed a prominent abdomen.

One week before admission anorexia, diarrhoea and vomiting returned.

Condition on Admission: A pale somewhat dehydrated child showing infantile proportions, being only 51 per cent. of her expected weight and 93 per cent. of expected height. Muscles hypotonic. Anterior fontanelle widely patent. Parietal bossing of skull.

Abdomen: very prominent, tympanitic. Motions loose, green and frequent.

Heart, Lungs, Nervous System, Urine - no abnormality.

Tuberculin Skin Tests (Mantoux and Pirquet) - negative.

CASE II (contd.).

SPECIAL INVESTIGATIONS:

X-ray skull: pituitary fossa normal.

Blood Examination: 13.9.33. R.B.C. = 3,350,000 per c.mm.
W.B.C. = 12,600 " "
Hb = 45%
Polymorphonuclear leucocytes - 45.5%
Small lymphocytes - 42.5%
Large lymphocytes - 5.0%.
Eosinophile myelocytes - 7.0%.

Biochemical Tests: See "B.G." in Sections II-V.

Course of Illness:

7/8/31-28/8/31:	R.H.S.C.	With intravenous glucose and a gradually increasing diet of protein milk the acute gastro-enteritis passed off in two weeks. Diet was increased to milk and sugar.
28/8/31-2/10/31:	Country Branch, Drumchapel.	Motions remained fairly frequent for a long time and after one month were typically 'coeliac,' being large, pale, and foul-smelling. With porridge and pudding added to the diet she gained steadily. Recurrence of diarrhoea and vomiting, however, entailed readmission to R.H.S.C.
2/10/31-1/12/31:	R.H.S.C.	For three weeks she had green stools and otitis media with irregular fever. She lost weight for a time then began to gain on a protein milk diet. A fuller coeliac diet was thereafter commenced (protein milk, curds, bananas) and progress was rapid till she developed measles and was transferred to Ruchill Hospital on 1/12/31.
15/12/31-4/3/32:	R.H.S.C.	Gain was steady for 3 weeks on coeliac diet, then she was in a poor state of health for the next two months with tonsillitis,/

CASE II (contd.).

		tonsillitis, cervical adenitis and crops of boils (Staph. aureus and Strept. infection). Collosal manganese injections (3 doses within 10 days) appeared to help the condition and by the end of February 1932 the boils were healing and appetite had improved.
4/3/32-6/1/33	Country Branch, Drumchapel.	On the same coeliac diet + Radiostol m.ii twice daily she gained slowly. Apart from occasional vomiting and constipation she had no untoward symptoms during her 9 months' residence. In spite of increase in the daily dietary to protein milk ⅔ x 5 x, curds from 1 pint milk and 2 bananas, however, she gained only 3 lbs. during the 9 months. Motions remained bulky.
6/1/33-18/1/33 6/2/33-17/2/33:	R.H.S.C.	At the age of 2½ years she was still 51 per cent. of her expected weight and 82 per cent. of expected height. She could sit up unsupported but could not stand. She was dismissed home but mother found dietary too difficult and after two weeks brought her back. One week later she was again dismissed home with whooping cough.
17/2/33-11/3/33:	Home.	Took diet (coeliac) fairly well and gained weight. Made good recovery from whooping-cough.
11/3/33-7/4/33:	R.H.S.C.	Did well for a week then suddenly dropped 1 lb. in weight, and developed loose motions. General condition was not much affected and after reduction in diet to protein milk only she rapidly recovered again.
7/4/33-8/9/33:	Country Branch, Drumchapel.	Weight continued to wax and wane for a month or two. On one occasion she ran an unexplained temperature for 4 days but was not upset. On 24/8/33 she reached her zenith weight of 8.75 K. and/

CASE II (contd.).

and never afterwards exceeded this weight. Diet was increased to skimmed milk (2 per cent.) ʒx 5 times, curds from 1 pint milk, 2 bananas and cornflakes once a day. Radiostol pellets, one twice daily, were also started in place of radiostol drops.

8/9/33-
2/11/33. R.H.S.C. Now aged 3 years she was 60 per cent. of her expected weight and 80 per cent. of her expected height. Her fontanelle was not closed and there was delayed ossification of wrist bone, though teeth were good. She looked well and with support could walk on a wide base. Her voice was high-pitched and she was able only to repeat small words said to her. Her hair was of very fine texture, and her eyes were large and dark. The abdomen was very prominent but no enlargement of liver or spleen could be found. The blood revealed a marked secondary anaemia. Apart from a slight attack of diarrhoea she remained comparatively well and gained weight for 6 weeks. Then for a metabolism experiment she was given antuitrin 1 c.cm. daily for two weeks but it was not completed as she developed a severe attack of diarrhoea and the diet had to be reduced to protein milk only. She had fever, leucocytosis and rapidly lost weight. Finally an acidotic attack supervened which failed to respond to intravenous glucose and she died within 24 hours.

POST-MORTEM FINDINGS: (J. W. S. Blacklock).

Macroscopic: Heart showed no marked fatty change.

Lungs were seat of hypostatic congestion.

Thymus, thoracic and mesenteric glands/

CASE II (contd.).

glands were not enlarged.

Intestine appeared normal apart from slight thinning of the walls.

Liver showed diffuse fatty change.

Gall-bladder contained abundant bile.

Kidneys showed slight fatty change.

Suprarenals, pituitary gland and pancreas appeared normal.

Microscopic: Liver - neutral fat (large and small globules), abundant but very little doubly refractile fat.
Cellular accumulations (lymphocytes with a few polymorphs) related to portal tract.
Liver cells healthy apart from fatty change.

Kidney. Glomeruli normal.
Very slight catarrhal change in tubules.
Fat (mostly neutral) in convoluted tubules, very little in collecting tubules and interstitial tissue.

Intestine (small bowel). Some cellular infiltration (round cell) in submucosa.

Pancreas. Islets appeared to be larger than normal but not increased in number.
Otherwise no abnormality of pancreatic tissue.

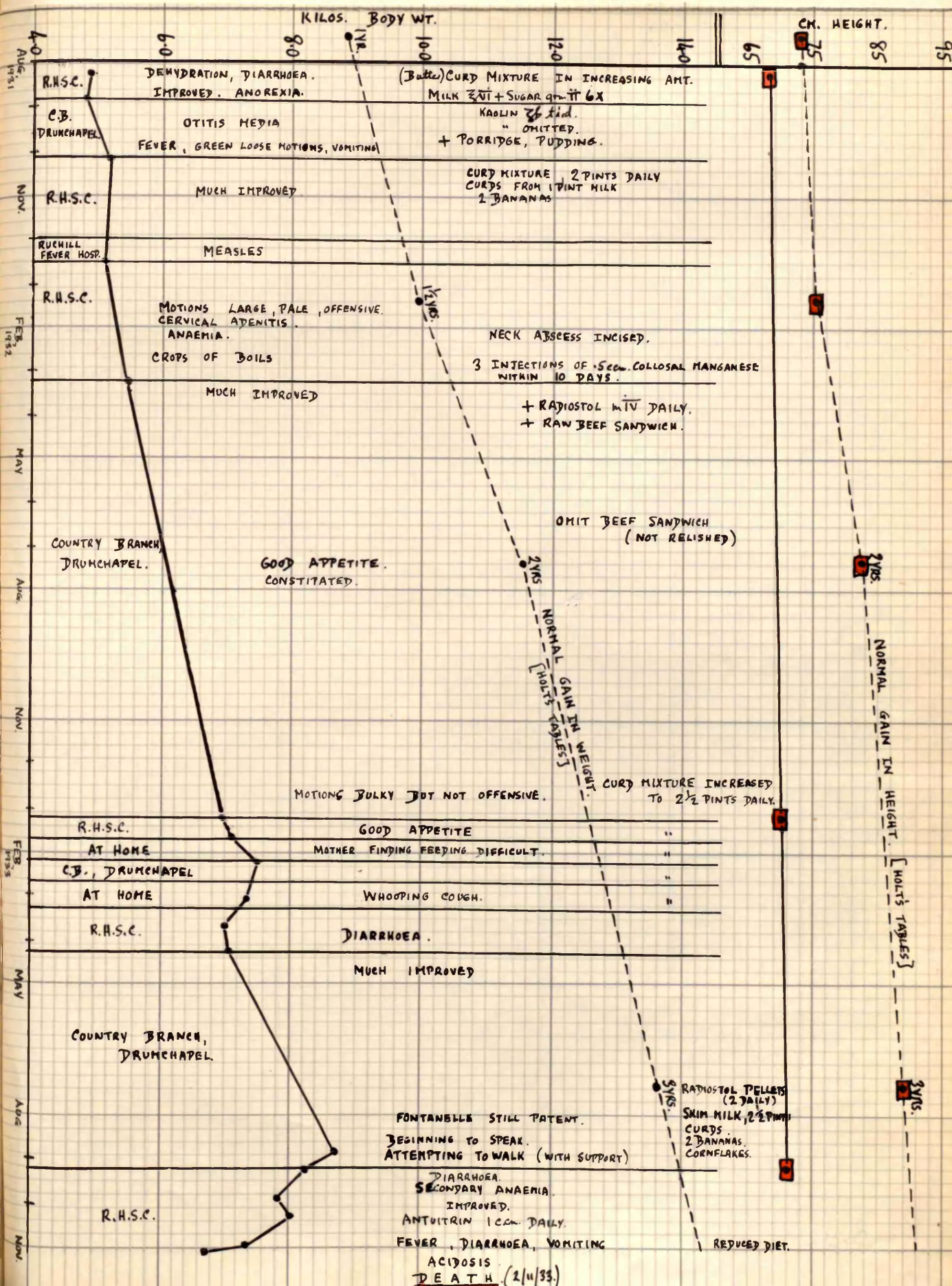
Suprarenals showed normal cortex and medulla.

Pituitary gland appeared to be normal, but this was difficult to assess.

PERSONAL COMMENT:

The increase in size of the pancreatic islets is an interesting finding. It has been shown by Anselmino, Herold and Hoffmann (Klin. Woch., Aug. 12, 1933, p. 1245) that administration of anterior pituitary lobe extract to rats caused an increase in number and size of the pancreatic islets

The other post-mortem findings of this case are not any more enlightening than those recorded in the literature of coeliac disease.


KILOS. BODY WT.
4·0
6·0
8·0
1 YR.
10·0
12·0
14·0
CM. HEIGHT.
55
75
85
95
AUG. 1931
NOV.
FEB. 1932
MAY
AUG.
NOV.
FEB. 1933
MAY
AUG
NOV.
R.H.S.C.
DEHYDRATION, DIARRHOEA. IMPROVED. ANOREXIA.
(Buttle) CURD MIXTURE IN INCREASING AMT.
MILK ℥VI + SUGAR grm. ii 6X
C.B. DRUMCHAPEL
OTITIS MEDIA
FEVER, GREEN LOOSE MOTIONS, VOMITING
KAOLIN ℥ss bid.
" OMITTED.
+ PORRIDGE, PUDDING.
R.H.S.C.
MUCH IMPROVED
CURD MIXTURE, 2 PINTS DAILY
CURDS FROM 1 PINT MILK
2 BANANAS
RUCHILL FEVER HOSP.
MEASLES
R.H.S.C.
1½ YRS.
MOTIONS LARGE, PALE, OFFENSIVE.
CERVICAL ADENITIS.
ANAEMIA.
CROPS OF BOILS
NECK ABSCESS INCISED.
3 INJECTIONS OF ·5ccm. COLLOSAL MANGANESE WITHIN 10 DAYS.
MUCH IMPROVED
+ RADIOSTOL mTV DAILY.
+ RAW BEEF SANDWICH.
OMIT BEEF SANDWICH (NOT RELISHED)
COUNTRY BRANCH, DRUMCHAPEL.
GOOD APPETITE.
CONSTIPATED.
2YRS.
NORMAL GAIN IN WEIGHT [HOLT'S TABLES]
2YRS.
NORMAL GAIN IN HEIGHT [HOLT'S TABLES]
MOTIONS BULKY BUT NOT OFFENSIVE.
CURD MIXTURE INCREASED TO 2½ PINTS DAILY.
R.H.S.C.
GOOD APPETITE "
AT HOME
MOTHER FINDING FEEDING DIFFICULT. "
C.B., DRUMCHAPEL
"
AT HOME
WHOOPING COUGH. "
R.H.S.C.
DIARRHOEA.
MUCH IMPROVED
COUNTRY BRANCH, DRUMCHAPEL.
3YRS.
3YRS.
RADIOSTOL PELLETS (2 DAILY)
SKIM MILK, 2½ PINTS
CURDS.
2 BANANAS.
CORNFLAKES.
FONTANELLE STILL PATENT.
BEGINNING TO SPEAK.
ATTEMPTING TO WALK (WITH SUPPORT)
DIARRHOEA.
SECONDARY ANAEMIA.
IMPROVED.
ANTUITRIN 1 ccm. DAILY.
R.H.S.C.
FEVER, DIARRHOEA, VOMITING
ACIDOSIS
REDUCED DIET.
DEATH. (2/11/33.)

CASE III.

Name:	William McKinlay.
Age:	$2^{6}/12$ years.
Admitted:	1/6/33.
Social Conditions:	Poor.
Family History:	Second child of family of 3 children - other two alive and well. Father and mother healthy.
Previous History:	Full time normal labour. Healthy at birth. Breast fed for 6 weeks then bottle-fed (cow's milk and sugar) entirely till 6 months; thereafter oat-flour porridge and puddings added. Throve well. Developed normally.
History of Illness:	At age of 2 years child had 'influenza' for 2 weeks. From that time he failed to thrive and became listless and irritable. Anorexia, occasional vomiting and 'thin, pale motions' became prominent symptoms. At times he complained of thirst. He was losing weight rapidly just prior to admission.
Condition on Admission:	A pale thin child, 66 per cent. of his expected weight and 89 per cent. of his expected height. Extremely irritable. Able at times to speak a few words. Wasted buttocks. Teeth good. Anterior fontanelle closed. Short, thin hair. Dusky pigmentation of skin of forehead and in front of ears.
	Abdomen: Very prominent - no masses palpable. Motions pale, offensive and bulky, not frequent.
	Heart, lungs, nervous system - no abnormality.
	Urine - no urobilin nor bile present.
	Tuberculin/

CASE III (contd.).

Tuberculin Skin Tests (Pirquet and Mantoux) - negative.

X-ray wrist - normal.

SPECIAL INVESTIGATIONS:

Blood pressure:		Systolic 78 mm. Hg.
X-ray skull:		Pituitary fossa normal.
Blood (26/6/33):		R.B.C. = 3,640,000 per c.mm. W.B.C. = 11,800 " " Hb. = 76% Ring-staining of red cells.
Biochemical Tests:		See "W. McK." in Sections II-V.
Course of illness:		
1/6/33- 7/7/33:	R.H.S.C.	During the first two weeks on light diet he continued to have 'coeliac' motions but not more than one daily. The diet was changed to milk without sugar but he did not improve in weight. Prior to dismissal to the Country Branch he was given a coeliac diet. (Sweet curd mixture ℥ x 5x, curds from 1 pint milk, 2 bananas and Radiostol m.ii twice daily).
7/7/33- 22/9/33:	Country Branch, Drum-chapel.	In the next 5 weeks he gained only 1 lb. in weight and motions remained offensive and occasionally loose. Radiostol drops were changed to pellets, one twice daily. Though gain in weight was slow his general appearance was better and he grew 3 cms. in height.
22/9/33- 26/10/33.	R.H.S.C.	No change in his condition resulted during the following month. The pulse, however, tended to be sub-normal. Injections of antuitrin were commenced in preparation for a metabolism experiment but these had to be discontinued as he developed paratyphoid/

CASE III (contd.).

		paratyphoid fever (Widal positive, but culture of stool and urine negative).
26/10/33-10/1/34:	Belvidere Fever Hospital.	The illness, according to reports given to the mother, was a mild one but on dismissal his general condition was poor and he was having foul frequent motions. He had not been given coeliac diet.
10/1/34-24/2/34:	At home:	Three days after dismissal from the Fever Hospital he reported at R.H.S.C. and it was found that he had not gained in weight nor height. He did not look well, was pale, listless and off his food. Motions were foul and loose. He was started on a diet of skimmed milk, curds and bananas with Radiostol pellets and during the next month his weight rose slightly. The motions improved and appetite returned but he remained pale and developed impetigo of the face and scalp. Frequently he complained of a sore tongue and on examination it was seen to be glazed and red. Culture of the faeces for B. typhosus was negative so he was readmitted to Hospital.
24/2/34-30/3/34:	R.H.S.C.	Now aged 3 years the child was still 65 per cent. of his expected weight and 90 per cent. of his expected height. He was apathetic and the wasting of the limbs was a marked contrast to the protuberant abdomen. Stools were frequent (two to three daily), pale bulky and oily. On a strictly measured diet of skimmed milk and curds for metabolism purposes he improved slightly and became less listless. Daily injections of antuitrin 1 c.cm. were given for three weeks, during the last 6 days of which he was on a metabolism bed, and/

CASE III (contd.).

and at the end of this time he was found to have gained 1 lb. in weight. His general condition was better, he was more lively and the motions though inclined to be loose and frequent (two to four daily) were less oily and less bulky. Metabolism revealed a 20 per cent. rise in fat absorption.

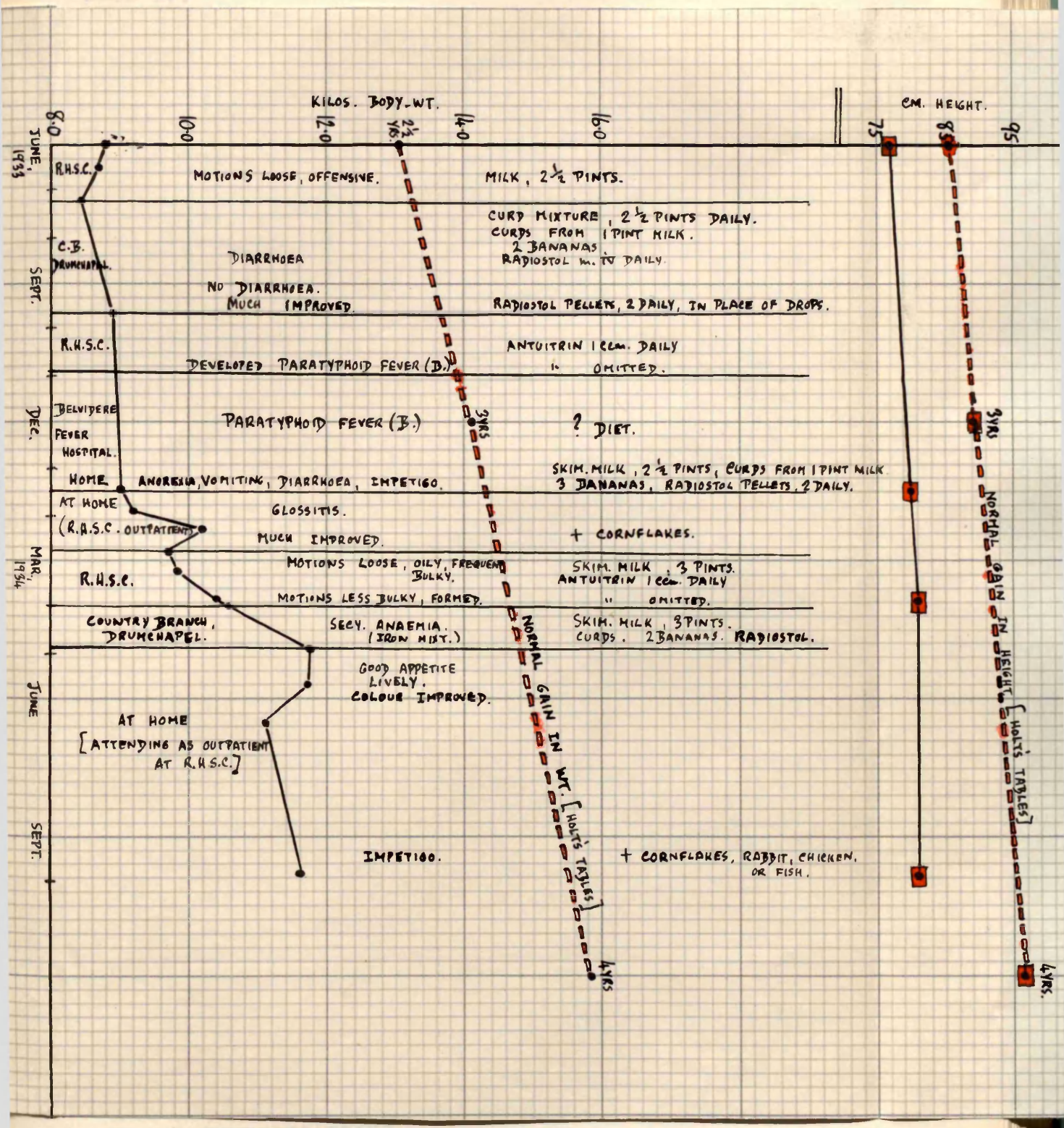
On a daily diet of skimmed milk, curds, 2 bananas and Radiostol pellets he was dismissed to the Country Branch on 30/3/34.

30/3/34-27/4/34:	Country Branch, Drumchapel.	With the above diet and an iron tonic (Fe et Ammon. Cit. gr. xv, $CuSO_4$ gr.1/100 t.i.d.) he gained 1 kilo in weight and colour improved.
27/4/34 onwards:	At home.	For 6 weeks he remained lively, appetite was good, and the motions though large and pale at times were not offensive nor frequent. Then for a short time he was irritable, had a troublesome cough and lost weight.

Condition on 25/9/34 (aet. $3^{11}/12$ years).

Child was pale and had impetigo of face and scalp. He was lively though irritable at times. Weight had been regained but percentage of expected weight was only 73. He had not grown any for past 6 months and was only 84 per cent. of his expected height. Cornflakes, rabbit, chicken, or fish were added to the dietary.

SEE GRAPH - next page.


KILOS. BODY-WT.
8·0
10·0
12·0
2¾ yrs.
14·0
16·0
CM. HEIGHT.
75
85
95
JUNE, 1933
R.H.S.C.
MOTIONS LOOSE, OFFENSIVE.
MILK, 2½ PINTS.
CURD MIXTURE, 2½ PINTS DAILY.
CURDS FROM 1 PINT MILK.
2 BANANAS.
RADIOSTOL m. IV DAILY.
C.B. DRUMCHAPEL.
SEPT.
DIARRHOEA
NO DIARRHOEA.
MUCH IMPROVED.
RADIOSTOL PELLETS, 2 DAILY, IN PLACE OF DROPS.
R.H.S.C.
ANTUITRIN 1 ccm. DAILY
" OMITTED.
DEVELOPED PARATYPHOID FEVER (B.)
BELVIDERE FEVER HOSPITAL.
DEC.
PARATYPHOID FEVER (B.)
3 YRS
? DIET.
HOME
ANOREXIA, VOMITING, DIARRHOEA, IMPETIGO.
SKIM. MILK, 2½ PINTS, CURDS FROM 1 PINT MILK
3 BANANAS, RADIOSTOL PELLETS, 2 DAILY.
AT HOME
(R.A.S.C. OUTPATIENT)
GLOSSITIS.
MUCH IMPROVED.
+ CORNFLAKES.
MAR. 1934
MOTIONS LOOSE, OILY, FREQUENT BULKY.
SKIM. MILK, 3 PINTS.
R.H.S.C.
ANTUITRIN 1 ccm. DAILY
MOTIONS LESS BULKY, FORMED.
" OMITTED.
COUNTRY BRANCH, DRUMCHAPEL.
SECY. ANAEMIA. (IRON MIST.)
SKIM. MILK, 3 PINTS.
CURDS. 2 BANANAS. RADIOSTOL.
NORMAL GAIN IN WT. [HOLT'S TABLES]
GOOD APPETITE
LIVELY.
COLOUR IMPROVED.
AT HOME
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
JUNE
SEPT.
IMPETIGO.
+ CORNFLAKES, RABBIT, CHICKEN, OR FISH.
4 YRS.
NORMAL GAIN IN HEIGHT [HOLT'S TABLES]
3 YRS
4 YRS.

CASE IV.

Name:	David McLaren.
Age:	$1^{10}/12$ years.
Admitted:	3/9/31.
Social Conditions:	Poor.
Family History:	First child. (Twins born in 1932 alive and well). Father and mother healthy.
Previous History:	Premature labour (8 months). Apparently healthy at birth. Breast-fed for 2 months then on diluted cow's milk till 1 year; thereafter Sister Laura's food commenced as he was not thriving. Cut first tooth at 10 months. Began to talk at 13 months. Was not attempting to walk at time of admission.
History of Illness:	Onset was insidious. At 18 months he began to lose weight, became listless and disinclined to play with toys. At times he was irritable. For one week before admission he had attacks of vomiting and refused to take food.
Condition on Admission:	Pale, thin child with evidence of dehydration: 63 per cent. of his expected weight and 96 per cent. of his expected height. Listless, at times irritable. Anterior fontanelle patent but teeth good. Superficial glands palpable. Abdomen: No record of any prominence. Motions large, pale, greasy. Heart, lungs, nervous system - no abnormality. Urine - no abnormality.

SPECIAL INVESTIGATIONS:

Blood pressure:	Systolic 66 mm. Hg.

CASE IV (contd.).

Urine: No urobilin nor bile.

Blood (10/7/33): R.B.C. = 4,240,000 per c.mm.
W.B.C. = 9,700 " "
Hb. = 48%

Differential Leucocyte Count:

Neutrophile polymorphs	42.7%
Small lymphocytes	49.2%
Large lymphocytes	5.5%
and Transitionals	2.6%

Ring-staining of red cells.

Biochemical Tests: See "D.McL." in Sections II-V.

Course of Illness:

3/9/31-18/10/31:	R.H.S.C.	After the first 10 days on a milk and sugar diet the child had diarrhoea and vomiting. This rapidly cleared up with restricted protein milk feeds. Later curds and bananas were added to the diet and apart from constipation he remained comparatively well. Dismissed home as chicken-pox contact.
18/10/31-29/10/31:	At home.	Coeliac diet. Diarrhoea and vomiting began on 28/10/31.
29/10/31-15/1/32:	R.H.S.C.	On a daily diet of butter curd mixture 240 cc. 5x, curds 2 x and 2 bananas he again recovered from gastro-enteritis, but did not gain much in weight.
15/1/32-26/5/32:	Country Branch, Drumchapel.	Radiostol m ii twice daily started. Apart from occasional vomiting and constipation in March 1932 he improved in general health. One scraped beef sandwich daily was added to the diet. On 26/5/32 he developed scarlet fever and was removed to Duntocher Fever Hospital. Here he was detained for more than 2 months - reason not known.

18/8/32/

CASE IV (contd.).

18/8/32-16/9/32:	R.H.S.C.	On dismissal from the Fever Hospital he was not eating well and soon afterwards diarrhoea and vomiting recurred. At the age of $2^{9}/12$ years he was 65 per cent. of his expected weight and only 87 per cent. of his expected height. He was of a dusky complexion, muscles were hypotonic, knee jerks were faint and a basal systolic murmur of the heart could be heard. Tuberculin Skin Tests (Pirquet and Mantoux) were negative. In 1 week he improved sufficiently to allow of a fat metabolism experiment being carried out.
16/9/32-6/1/33:	Country Branch, Drumchapel.	Motions remained large and loose for the first 3 weeks. Diet consisted of sweet curd mixture 210 c.cms. 5 x daily, curds from 1 pint milk, 2 bananas and Radiostol m ii twice daily. After 3 months the curd mixture was increased to 300 c.cms. 5 x.
6/1/33-18/1/33:	R.H.S.C.	Gain in weight was rapid and as he was eating well he was dismissed home on above diet.
18/1/33-3/3/33:	At home.	Developed whooping cough and lost appetite. Had occasional diarrhoea, flatulence and colicky pains in the abdomen.
3/3/33-7/4/33:	R.H.S.C.	On admission, he was pale; abdomen was very prominent; tonsils were enlarged. He had not gained any weight. Diet commenced as above and at the end of a month, motions were of better consistence and he was putting on weight again.
7/4/33-26/5/33:	Country Branch, Drumchapel.	Remained comparatively well but weight was stationary. Motions 2 daily and constipated.
26/5/33-14/7/33:	R.H.S.C.	Diet as before. X-ray of wrist on 5/6/33/

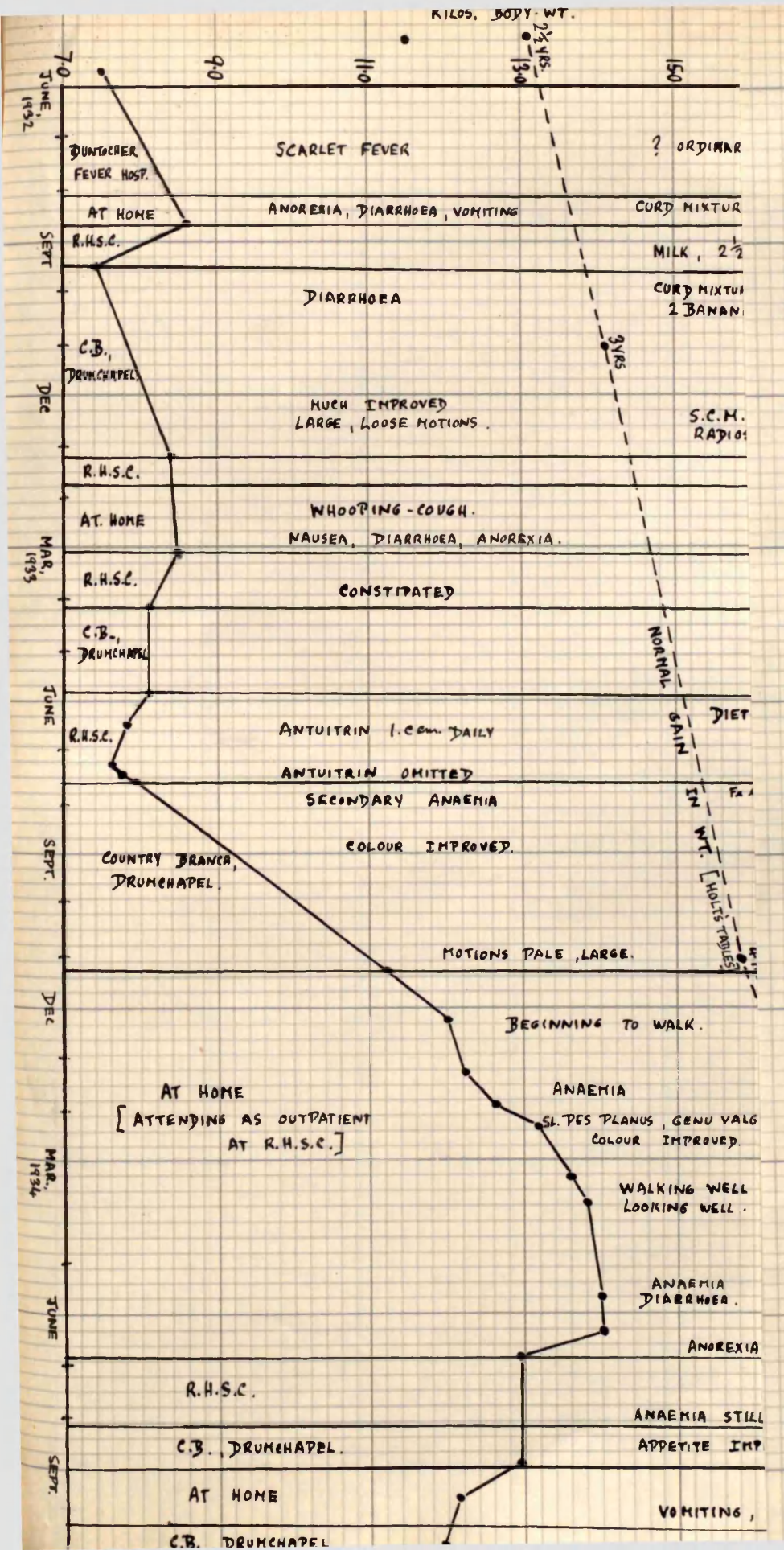
CASE IV (contd.).

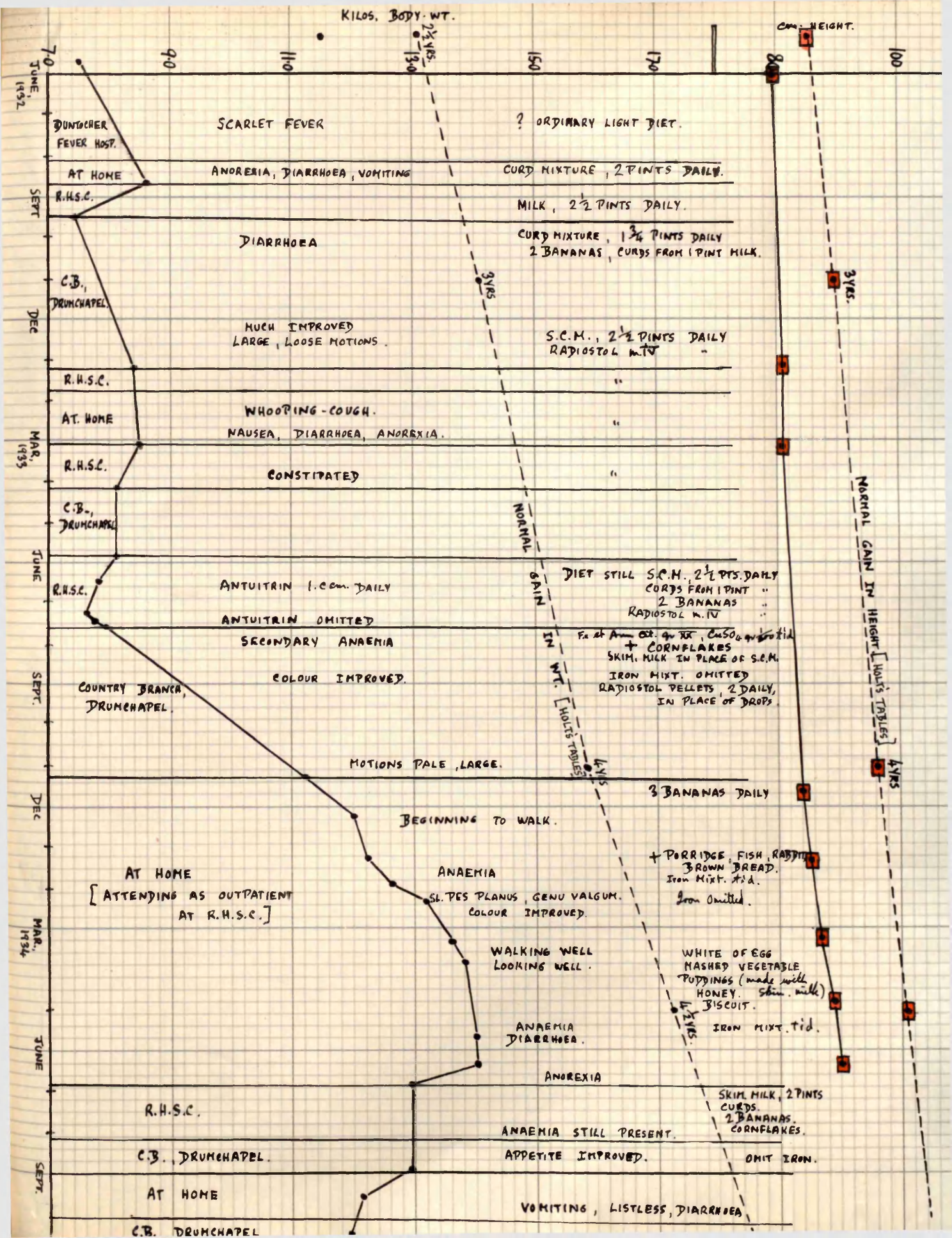
		5/6/33 revealed delayed ossification but no rickets. Daily injections of antuitrin 1 c.cm. for one month did not improve the weight chart. Stools remained constipated.
14/7/33-10/11/33:	Country Branch, Drumchapel.	Daily diet was skimmed milk 300 c.cm. 5 x, 2 bananas, cornflakes and curds from 1 pink milk; also Radiostol pellets, one twice daily. Severe secondary anaemia was treated with Ferri et Ammon. Cit. gr XX, $CuSO_4$ gr. 1/200 t.i.d. for 1 month. At the end of his stay he was looking well, taking his diet eagerly and had gained 7 lbs in weight and 3 cms. in height.
10/11/33-24/7/34:	At home.	During the next 3 months he reported at R.H.S.C. at fortnightly intervals and showed a steady gain in weight and height. The diet was supplemented gradually, oatflour porridge, fish and rabbit being introduced. Radiostol pellets were continued, one twice daily. As he remained pale, another course of iron treatment was given for 3 weeks. Motions were pale, bulky and sometimes offensive - 1 to 2 daily. In the following 5 months he was observed at intervals of 3-4 weeks. At the end of March he was walking well apart from slight pes planus of left foot. Mashed vegetable (carrot, turnip, potato) was introduced to the daily dietary, also an occasional biscuit and white of egg. He continued to gain in weight and height and in spite of Radiostol pellets, X-ray of wrist revealed slight rickets (loss of convex outline of bone) and ossification of a 2 years' child. At the age of 4½ years he was 80 per cent. of his expected weight and 88 per cent. of his expected height. His zenith weight was 14.1 K. on 9/6/34. He became more/

CASE IV (contd.).

		more and more lively, steadier on his feet; the abdomen was less prominent and the muscles less flabby. The distribution of fat was that of a case of mild Fröhlich's Syndrome. In July, 1934, he had a relapse with diarrhoea, anorexia and loss of weight.
24/7/34-10/8/34:	R.H.S.C.	On a diet of skimmed milk and curds he recovered in 1 week. In the next 10 days the diet was gradually restored to that previous to the relapse. Severe secondary anaemia was again found from blood examination and a course of iron treatment given accordingly.
28/8/34-31/8/34:	Country Branch, Drumchapel.	Remained comparatively well, but weight was stationary.
30/8/34-18/9/34:	At Home.	Had a relapse - vomiting, loss of weight.
18/9/34-28/9/34:	R.H.S.C.	Rapidly recovered and was sent to the Country Branch on a diet of skimmed milk, cornflakes, curds, 3 bananas and Radiostol, two pellets daily.

SEE GRAPH - next page.


KILOS. BODY-WT.
7·0
9·0
11·0
2½ YRS — 13·0
15·0
JUNE, 1932.
DUNTOCHER FEVER HOSP.
SCARLET FEVER
? ORDINAR
AT HOME
ANOREXIA, DIARRHOEA, VOMITING
CURD MIXTUR
R.H.S.C.
MILK, 2½
SEPT.
DIARRHOEA
CURD MIXTU
2 BANAN
3 YRS
C.B., DRUMCHAPEL.
DEC
MUCH IMPROVED
LARGE, LOOSE MOTIONS.
S.C.M.
RADIO
R.H.S.C.
AT HOME
WHOOPING-COUGH.
NAUSEA, DIARRHOEA, ANOREXIA.
MAR. 1933
R.H.S.C.
CONSTIPATED
C.B., DRUMCHAPEL
NORMAL
GAIN
IN
WT.
[HOLT'S TABLES]
JUNE
DIET
R.H.S.C.
ANTUITRIN 1 c.cm. DAILY
ANTUITRIN OMITTED
SECONDARY ANAEMIA
COLOUR IMPROVED.
SEPT.
COUNTRY BRANCH, DRUMCHAPEL.
MOTIONS PALE, LARGE.
DEC
BEGINNING TO WALK.
AT HOME
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
ANAEMIA
SL. PES PLANUS, GENU VALG
COLOUR IMPROVED.
MAR. 1934
WALKING WELL
LOOKING WELL.
ANAEMIA
DIARRHOEA.
JUNE
ANOREXIA
R.H.S.C.
ANAEMIA STILL
C.B., DRUMCHAPEL.
APPETITE IMP
SEPT.
AT HOME
VOMITING,
C.B. DRUMCHAPEL


KILOS. BODY-WT.
CM. HEIGHT.
7·0
9·0
11·0
13·0
15·0
17·0
80
100
2½ YRS.
3 YRS.
4 YRS.
JUNE, 1932.
SEPT.
DEC
MAR, 1933
JUNE
SEPT.
DEC
MAR. 1934
JUNE
SEPT.
DUNTOCHER FEVER HOSP.
SCARLET FEVER
? ORDINARY LIGHT DIET.
AT HOME
ANOREXIA, DIARRHOEA, VOMITING
CURD MIXTURE, 2 PINTS DAILY.
R.H.S.C.
MILK, 2½ PINTS DAILY.
DIARRHOEA
CURD MIXTURE, 1¾ PINTS DAILY
2 BANANAS, CURDS FROM 1 PINT MILK.
C.B., DRUMCHAPEL.
MUCH IMPROVED
LARGE, LOOSE MOTIONS.
S.C.M., 2½ PINTS DAILY
RADIOSTOL m.IV
R.H.S.C.
"
AT. HOME
WHOOPING-COUGH.
NAUSEA, DIARRHOEA, ANOREXIA.
"
R.H.S.C.
CONSTIPATED
"
C.B., DRUMCHAPEL
NORMAL GAIN IN WT. [HOLT'S TABLES]
NORMAL GAIN IN HEIGHT [HOLT'S TABLES]
R.H.S.C.
ANTUITRIN 1 c.cm. DAILY
DIET STILL S.C.M., 2½ PTS. DAILY
CURDS FROM 1 PINT "
2 BANANAS "
RADIOSTOL m.IV
ANTUITRIN OMITTED
SECONDARY ANAEMIA
Fe et Am. Cit. gr. XX, CuSO4 gr. ½ tid
+ CORNFLAKES
SKIM. MILK IN PLACE OF S.C.M.
IRON MIXT. OMITTED
COLOUR IMPROVED.
RADIOSTOL PELLETS, 2 DAILY,
IN PLACE OF DROPS.
COUNTRY BRANCH, DRUMCHAPEL.
MOTIONS PALE, LARGE.
3 BANANAS DAILY
BEGINNING TO WALK.
+ PORRIDGE, FISH, RABBIT,
BROWN BREAD.
Iron Mixt. tid.
AT HOME
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
ANAEMIA
SL. PES PLANUS, GENU VALGUM.
COLOUR IMPROVED.
Iron Omitted.
WALKING WELL
LOOKING WELL.
WHITE OF EGG
MASHED VEGETABLE
PUDDINGS (made with HONEY. Skim. milk)
BISCUIT.
IRON MIXT. tid.
ANAEMIA
DIARRHOEA.
ANOREXIA
SKIM. MILK, 2 PINTS
CURDS.
2 BANANAS.
CORNFLAKES.
R.H.S.C.
ANAEMIA STILL PRESENT.
C.B., DRUMCHAPEL.
APPETITE IMPROVED.
OMIT IRON.
AT HOME
VOMITING, LISTLESS, DIARRHOEA
C.B. DRUMCHAPEL

CASE V.

Name:	Mary O'Brien.
Age:	$1^{6}/12$ years.
Admitted:	30/5/32.
Social Conditions:	Poor.
Family History:	Father and mother apparently healthy. 8th child; 3 died in infancy; one brother has had rheumatic fever and pneumonia.
Previous History:	Premature labour (7 months). Small baby, cyanosed and feeble. Failed to gain with breast-feeding during first 3 months. Throve better on Berina food till 9 months and thereafter on ordinary foods. Measles at 13 months undermined her health.
History of Illness:	Following on "recovery" from measles, child had diarrhoea and vomiting for 2 weeks. She lost weight, became irritable during the day and restless at night. Motions later were constipated and occasionally blood-streaked. Anorexia developed two weeks prior to admission.
Condition on Admission:	Pale, irritable child of infantile proportions, being 70 per cent. of her expected weight and 94 per cent. of her expected height. Anterior fontanelle patent. X-ray wrist - no rickets. Abdomen: Not unduly prominent. Motions normal in colour and consistency. Lungs: Cough present. Rhonchi at both bases. Heart, Nervous System, Urine - No abnormality. Tuberculin Skin Tests (Mantoux and Pirquet) - negative.

SPECIAL/

CASE V (contd.).

SPECIAL INVESTIGATIONS:

Blood Pressure: 58 Systolic, 30 Diastolic.

X-ray Skull: Pituitary fossa normal.

X-ray Wrist (29/3/34): Slight rickets, late ossification.

Blood (20/10/33): R.B.C. = 3,980,000 per c.mm.
W.B.C. = 6,700 " "
Hb. = 52%

Differential Leucocyte Count: Neutrophile polymorphs 44%
Large lymphocytes 36%
Small lymphocytes 15%
Neutrophile myelocytes 3%
Eosinophile myelocytes 2%
Red cells showed ring-staining.

Course of Illness:

30/5/32-10/6/32.	R.H.S.C.	In first week she regained her appetite and chest became clear. Weight remained stationary. Diet was gradually increased from milk and sugar only to milk, pudding and porridge.
10/6/32-30/6/32:	Country Branch, Drumchapel,	Appetite was poor at first. Syr. Ferri Phos. Co. ℥ p t.i.d. was tried without much improvement. Then she began to eat more food and gained 11 ozs.
30/6/32-4/8/32:	At home.	Was well for 1 month then diarrhoea began. Motions were large, light-brown in colour, offensive and numbered four daily.
4/8/32-9/9/32:	R.H.S.C.	On milk diet (+ sugar) child's condition did not improve - anorexia, vomiting and 'coeliac' motions were in evidence. Coeliac diet commenced 24/8/32 (Sweet curd mixture 240 c.cm. 5 x, curds from 1 pint milk, 2 bananas daily). Weight continued to fall.
9/9/32-13/6/33:	Country Branch, Drumchapel.	During the next 4 months she took the diet reluctantly, did not gain weight and motions remained large, pale and sometimes loose. Thereafter stools and/

CASE V (contd.).

		and appetite improved. Radiostol m ii 2 x commenced. Bananas increased to 4 daily. She gained 1½ lbs in last 2 months of her stay.
13/6/33-7/7/33:	R.H.S.C.	Improvement in general appearance of the child occurred. Motions were formed but pale and bulky.
7/7/33-6/10/33:	Country Branch, Drumchapel.	Sweet curd mixture increased to 300 c.cm. 5 x, otherwise diet kept as above. Radiostol pellets, 2 daily, in place of drops. Pulse rate was often subnormal. Occasionally she was constipated. Gained 2 lbs during the 3 months. Cornflakes were added to the diet and sweet curd mixture replaced by skimmed milk.
6/10/33-16/11/33:	R.H.S.C.	Convalescence was not interrupted by a paratyphoid outbreak in the ward. Widal test, stool and urine cultures were negative. Just prior to dismissal she was put on Trufood separated milk (1 oz. to ½ pint water 5 x) in place of skimmed milk, and given a 3 weeks' course of iron as the blood revealed a marked secondary anaemia.
16/11/33 onwards:	At home.	At the age of 3 years in December 1933 she was 68 per cent. of her expected weight and 86 per cent. of her expected height. She was beginning to walk and looked well. Motions were normal in colour and slightly constipated. Orange juice was started twice weekly, and the supply of cornflakes increased. Gradually oatflour porridge, fish, rabbit, meat juice, apples, brown bread were added and she gained weight steadily. For 1 week in February she had an attack of bronchitis and at that time the diet was reduced. Recovery was rapid and she was getting on well again when in March 1934 she developed a second attack. This caused a loss in weight; glossitis was present and she was confined/

CASE V (contd.).

confined to bed for 2 weeks. The diet was temporarily reduced to skimmed milk, bananas and curds. At the end of 1 month she began to regain weight, appetite, etc. Growth was also rapid - at the end of 4 months after dismissal from hospital she had grown 5.5 cm. and put on 6 lbs. At the age of $3\frac{1}{2}$ years in June 1934, she was 86 per cent. of her expected weight and 90 per cent. of her expected height.

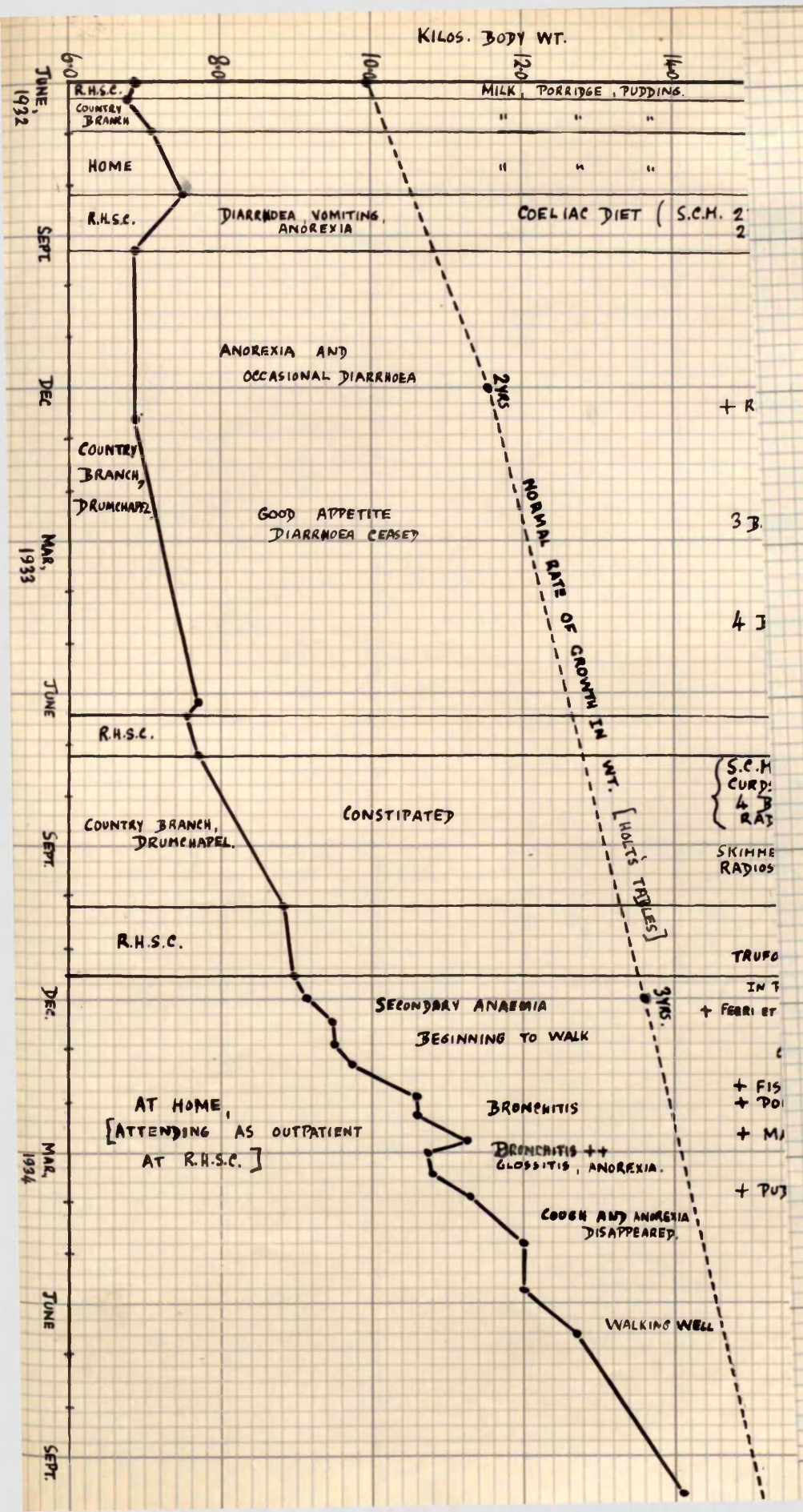
Condition on 25/9/34 (aet. $3^{9}/12$ years).

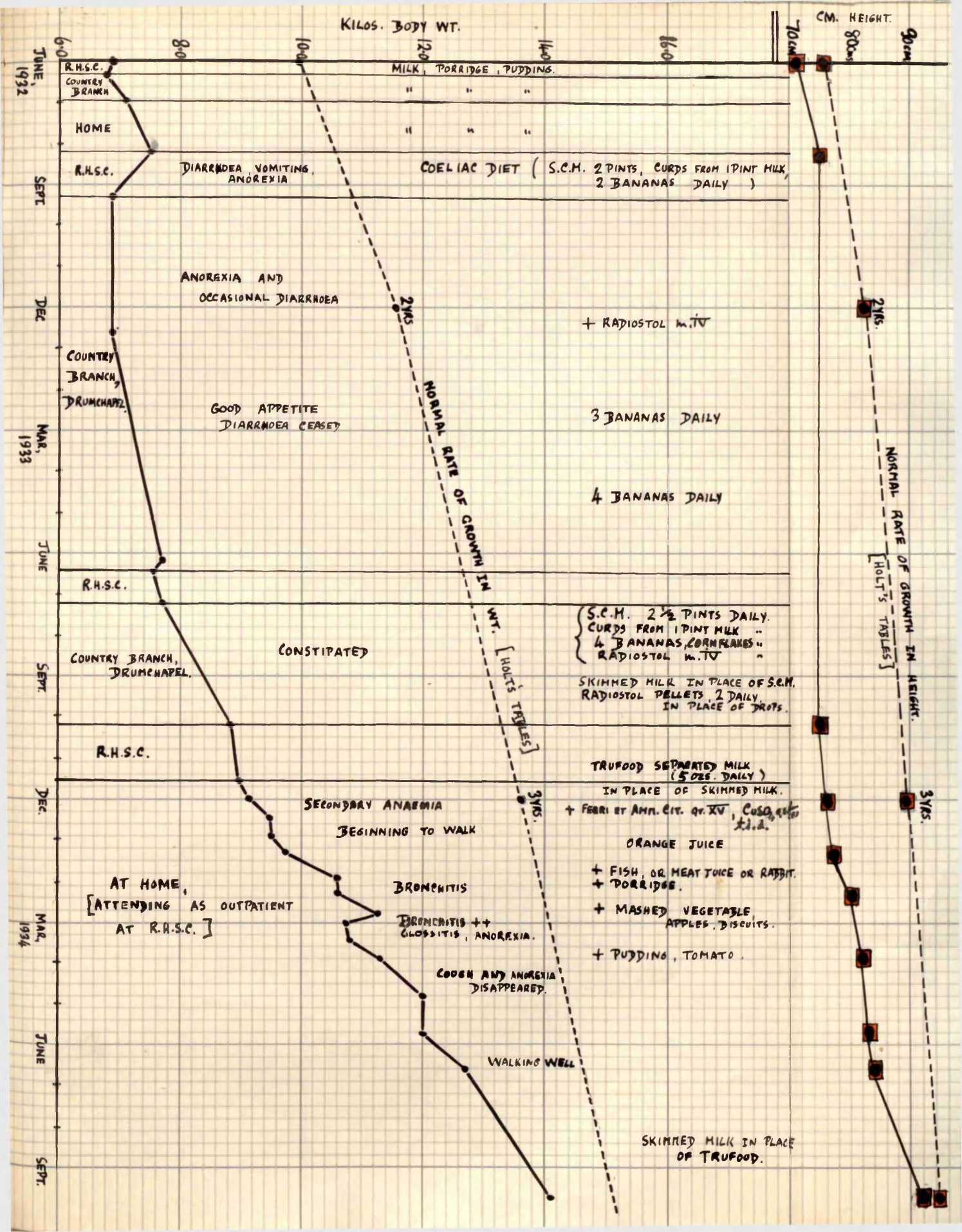
Child was looking well, walked well and talked quite intelligently. Her hair was growing. Teeth were become carious. She was now 91 per cent. of her expected weight and 97 per cent. of her expected height (During 3 months she had gained 8 cm. in height). Motions were sometimes constipated and large but not offensive nor frequent, and the colour light brown. Diet had not been altered.

PERSONAL COMMENT:

This patient showed most striking progress during the last 9 months at home - the advance far exceeded that of any of the other patients during a similar period, as will be seen from the following weight graph.

SEE GRAPH - next page.


KILOS. BODY WT.
6·0
8·0
10·0
12·0
14·0
JUNE, 1932
SEPT.
DEC
MAR, 1933
JUNE
SEPT.
DEC.
MAR, 1934
JUNE
SEPT.
R.H.S.C.
COUNTRY BRANCH
MILK, PORRIDGE, PUDDING.
" " "
HOME
" " "
R.H.S.C.
DIARRHOEA, VOMITING, ANOREXIA
COELIAC DIET (S.C.H. 2
2
ANOREXIA AND OCCASIONAL DIARRHOEA
2YRS
+ R
COUNTRY BRANCH, DRUMCHAPEL
GOOD APPETITE
DIARRHOEA CEASED
3 B
4 J
NORMAL RATE OF GROWTH IN WT. [HOLT'S TABLES]
R.H.S.C.
S.C.H
CURD
4 B
RA
CONSTIPATED
COUNTRY BRANCH, DRUMCHAPEL.
SKIMME
RADIOS
R.H.S.C.
TRUFO
IN T
3YRS.
SECONDARY ANAEMIA
+ FERRI ET
BEGINNING TO WALK
+ FIS
+ DO
AT HOME, [ATTENDING AS OUTPATIENT AT R.H.S.C.]
BRONCHITIS
+ M
BRONCHITIS ++ GLOSSITIS, ANOREXIA.
+ PU
COUGH AND ANOREXIA DISAPPEARED.
WALKING WELL


KILOS. BODY WT.
CM. HEIGHT.
6·0
8·0
10·0
12·0
14·0
16·0
70cms.
80cms.
90cms.
JUNE, 1932
SEPT.
DEC.
MAR, 1933
JUNE
SEPT.
DEC.
MAR, 1934
JUNE
SEPT.
R.H.S.C.
COUNTRY BRANCH
HOME
R.H.S.C.
MILK, PORRIDGE, PUDDING.
" " "
" " "
DIARRHOEA, VOMITING, ANOREXIA.
COELIAC DIET (S.C.M. 2 PINTS, CURDS FROM 1 PINT MILK, 2 BANANAS DAILY)
ANOREXIA AND OCCASIONAL DIARRHOEA
2YRS.
NORMAL RATE OF GROWTH IN WT. [HOLT'S TABLES]
+ RADIOSTOL m.IV
COUNTRY BRANCH, DRUMCHAPEL.
GOOD APPETITE
DIARRHOEA CEASED
3 BANANAS DAILY
4 BANANAS DAILY
R.H.S.C.
CONSTIPATED
COUNTRY BRANCH, DRUMCHAPEL.
S.C.M. 2½ PINTS DAILY.
CURDS FROM 1 PINT MILK "
4 BANANAS, CORNFLAKES "
RADIOSTOL m.IV "
SKIMMED MILK IN PLACE OF S.C.M.
RADIOSTOL PELLETS 2 DAILY IN PLACE OF DROPS.
R.H.S.C.
TRUFOOD SEPARATED MILK (5 OZS. DAILY) IN PLACE OF SKIMMED MILK.
+ FERRI ET AMM. CIT. gr. XV, CUSO4 gr. 1/10 t.i.d.
SECONDARY ANAEMIA
BEGINNING TO WALK
3YRS.
ORANGE JUICE
+ FISH, OR MEAT JUICE OR RABBIT.
+ PORRIDGE.
+ MASHED VEGETABLE, APPLES, BISCUITS.
+ PUDDING, TOMATO.
AT HOME, [ATTENDING AS OUTPATIENT AT R.H.S.C.]
BRONCHITIS
BRONCHITIS ++ GLOSSITIS, ANOREXIA.
COUGH AND ANOREXIA DISAPPEARED.
WALKING WELL
SKIMMED MILK IN PLACE OF TRUFOOD.
2YRS.
NORMAL RATE OF GROWTH IN HEIGHT. [HOLT'S TABLES]
3YRS.

CASE VI.

Name:	Phyllis Sneddon.
Age:	2 years.
Admitted:	22/8/32.
Social Conditions:	Good.
Family History:	Father and mother healthy. Second child of family of three. Other two alive and well.
Previous History:	Full time breech birth. Apparently healthy (weight 8 lbs). Breast fed for 3 months then given diluted cow's milk till 9 months and throve well. Measles at 16 months - no after-effects. Was walking well at 18 months.
History of Illness:	Onset was insidious. At $1^{9}/12$ years she began to lose weight, became listless and irritable, and sometimes vomited undigested material (frequently part of a previous meal, even 4 hours before). Bouts of diarrhoea alternated with constipation. She was easily tired by walking, and feet often felt cold.
Condition on Admission:	A pale "delicate-looking" child, very dwarfed (being only 60 per cent. of her expected weight and 93 per cent. of her expected height). Skin dry. Anterior fontanelle patent but teeth good. Superficial glands palpable. Abdomen - prominent. Motions large, offensive and pale. Heart, lungs, nervous system - no abnormality. Urine - no urobilin. Tuberculin Skin Tests (Mantoux and Pirquet) - negative.

SPECIAL/

CASE VI (contd.).

SPECIAL INVESTIGATIONS:

Blood Pressure:	Systolic 50-60 mm. Hg.
Urine:	No urobilin (several specimens tested).
Blood (6/6/33):	R.B.C. 3,770,000 per c.mm. W.B.C. 7,100 " " Hb. 60% Red cells quite well stained.
(20/11/33):	R.B.C. 4,430,000 per c.mm. W.B.C. 10,300 " " Hb. 52% Red cells show ring-staining. Reticulocytes 1.6%
(11/12/33): After 1 week of iron treatment.	R.B.C. 5,030,000 per c.mm. W.B.C. 11,400 " " Hb. 65% Reticulocytes 4.5%
(5/1/34): After 1 month of iron treatment.	R.B.C. 5,090,000 per c.mm. W.B.C. 14,700 " " Hb. 76%
Biochemical Tests:	See 'P.S.' in Sections II-V.

Course of Illness:

22/8/32-9/9/32:	R.H.S.C.	With a diet of milk, bananas, and finally porridge and pudding the stools improved and ultimately were constipated.
9/9/32-20/1/33:	Country Branch, Drumchapel.	Coeliac diet was instituted (Sweet curd mixture ½ x 5 x, 2 bananas, curds from 1 pint milk). This she took reluctantly and at the end of a week skimmed milk was tried in place of sweet curd mixture. The curds were omitted and porridge was added twice daily. Gradually her appetite improved and the motions which at first were large and offensive became less so. At the end of 3 months she was beginning to gain weight/

CASE VI (contd.).

		weight when she developed scarlet fever.
20/1/33- 14/4/33:	Duntocher Fever Hospital.	Otitis media prolonged her stay here. Feeding was difficult. She was given undiluted milk, 2 bananas and pudding but preferred 'sweet things.'
14/4/33- 8/5/33:	R.H.S.C.	On admission child looked ill, was listless, and refused to walk. She had severe diarrhoea (5 to 6 motions per day). Emaciation of limbs especially was marked (She was only 54 per cent. of her expected weight and 93 per cent. of her expected height). Tongue was coated and skin dusky coloured. There were cracks at the corners of the mouth. Heart, lungs and nervous system revealed no abnormality but the abdomen was very prominent. She was given a diet of 2% milk ʒ x 5 x and 2 bananas. Two weeks later she developed a cervical gland abscess which required incision and a few days afterwards she took chicken-pox.
8/5/33- 25/5/33:	At home.	Chicken-pox was mild. Diarrhoea was troublesome.
25/5/33- 14/7/33:	R.H.S.C.	Now aged $2^{9}/12$ years. She was only 52 per cent. of her expected weight and still 93 per cent. of her expected height. Emaciation was in striking contrast to her large abdomen. The diet given during this period at R.H.S.C. was skimmed milk 1500 c.cm. daily in view of a fat metabolism experiment with antuitrin. As mentioned in Section V there was no gain in weight after 3 weeks' daily injections of antuitrin 1 c.cm. but as much as 93.3 per cent. of the fat ingested was being absorbed in the last week of the experiment.
14/7/33- 17/11/33:	Country Branch, Drumchapel.	During the next 6 weeks the daily diet consisted of skimmed milk 1500 c.cm., 2 bananas, curds from 1 pint milk, marmite ʒ iii and 2 Radiostol pellets. Whether due to the remote effect/

CASE VI (contd.).

		effect of the antuitrin treatment, the change of environment or the marmite or to all three together, the general health began to improve by leaps and bounds. She gained over 4 lbs. in weight. In the week ending 5/9/33 she put on a further 2 lbs. An attack of diarrhoea and vomiting arrested the rapid convalescence but she did not lose any ground in the next 2 months. Her colour was good. She was attempting to walk, spoke a few words at a time and was contented. The anterior fontanelle was now closed and her teeth good.
17/11/33- 21/1/34:	R.H.S.C.	At the age of $3^{3}/12$ years she was now 71 per cent. of her expected weight but only 89 per cent. of her expected height (she was no taller than at $2^{8}/12$ years). In spite of her good colour, blood examination revealed only 52% Hb. This was increased to 76% by 1 month's treatment with iron. Cornflakes and raw beef sandwiches were added to the diet and at the end of two months rabbit, fish and chicken. In January she had a mild upper respiratory infection which cleared up in 10 days. It was accompanied by some vomiting. From that time on she improved again and though the gain in weight was slight she grew one inch in height. With massage her legs became stronger and she was able to walk a little. X-ray of wrist on 22/1/34 revealed delayed ossification ($1^{9}/12$ years), thin bones and numerous transverse striations ('tree-rings' described by Parsons), but no evidence of rickets.
22/1/34 onwards:	At home.	The diet was supplemented by porridge, white of egg and an occasional biscuit. She began to walk better and with less genu valgum than at first. She reported at R.H.S.C. at 2-4 weeks' intervals and showed a steady/

CASE VI (contd.).

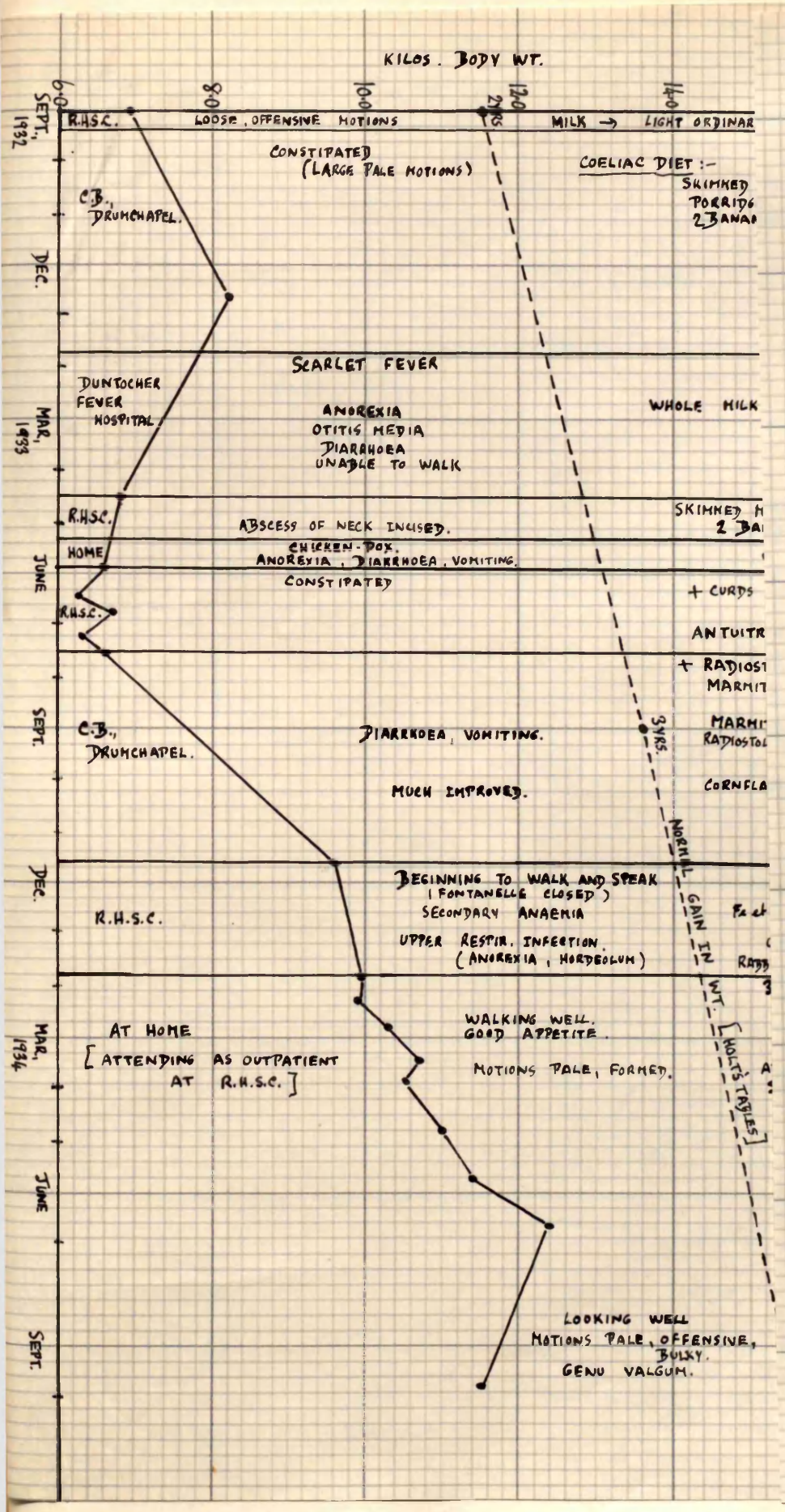
steady gain in weight and height. From 29/3/34 she was taking 3 pints skimmed milk and 4 bananas daily. An X-ray of wrist on 29/3/34 showed no advance from that of 22/1/34. The motions were often large, pale and foul-smelling, numbering 2 or 3 per day.

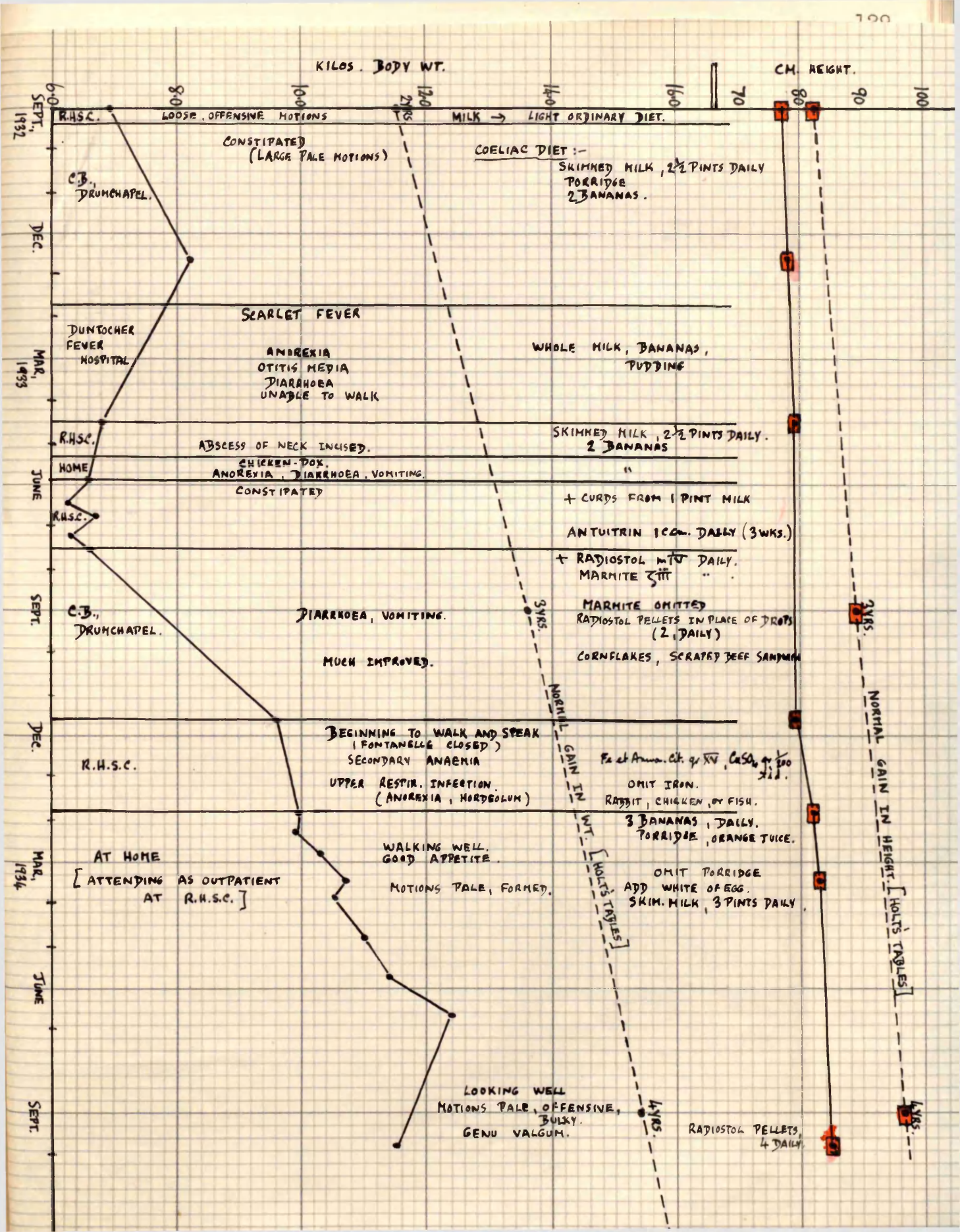
Condition on 25/9/34 (aet. $4\frac{2}{12}$ years).

Child looked well, was lively and spoke intelligently. Her hair was growing long though still of very fine texture. Genu valgum was again visible when she walked. She was 73 per cent. of her expected weight and 88 per cent. of her expected height.

Radiostol pellets were increased to 4 daily.

SEE GRAPH - next page.


KILOS. BODY WT.
6·0
8·0
10·0
12·0
14·0
SEPT. 1932
DEC.
MAR. 1933
JUNE
SEPT.
DEC.
MAR. 1934
JUNE
SEPT.
R.H.S.C.
LOOSE, OFFENSIVE MOTIONS
2YRS.
MILK → LIGHT ORDINAR
CONSTIPATED
(LARGE PALE MOTIONS)
COELIAC DIET :-
SKIMMED
PORRIDG
2 BANA
C.B., DRUMCHAPEL.
SCARLET FEVER
DUNTOCHER FEVER HOSPITAL.
ANOREXIA
OTITIS MEDIA
DIARRHOEA
UNABLE TO WALK
WHOLE MILK
R.H.S.C.
ABSCESS OF NECK INCISED.
SKIMMED M
2 BA
HOME
CHICKEN-POX.
ANOREXIA, DIARRHOEA, VOMITING.
CONSTIPATED
+ CURDS
R.H.S.C.
ANTUITR
+ RADIOST
MARMIT
C.B., DRUMCHAPEL.
DIARRHOEA, VOMITING.
3YRS.
MARMI
RADIOSTOL
MUCH IMPROVED.
CORNFLA
NORMAL
BEGINNING TO WALK AND SPEAK
(FONTANELLE CLOSED)
SECONDARY ANAEMIA
R.H.S.C.
UPPER RESPIR. INFECTION.
(ANOREXIA, HORDEOLUM)
GAIN IN WT. [HOLT'S TABLES]
AT HOME
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
WALKING WELL.
GOOD APPETITE.
MOTIONS PALE, FORMED.
LOOKING WELL
MOTIONS PALE, OFFENSIVE, BULKY.
GENU VALGUM.


KILOS. BODY WT.
6·0
8·0
10·0
12·0
14·0
16·0
CM. HEIGHT.
70
80
90
100
SEPT., 1932
DEC.
MAR., 1933
JUNE
SEPT.
DEC.
MAR., 1934
JUNE
SEPT.
R.H.S.C.
LOOSE, OFFENSIVE MOTIONS
2 YRS.
MILK → LIGHT ORDINARY DIET.
CONSTIPATED (LARGE PALE MOTIONS)
COELIAC DIET :-
SKIMMED MILK, 2½ PINTS DAILY
PORRIDGE
2 BANANAS.
C.B., DRUMCHAPEL.
SCARLET FEVER
DUNTOCHER FEVER HOSPITAL.
ANOREXIA
OTITIS MEDIA
DIARRHOEA
UNABLE TO WALK
WHOLE MILK, BANANAS, PUDDING
R.H.S.C.
ABSCESS OF NECK INCISED.
SKIMMED MILK, 2½ PINTS DAILY.
2 BANANAS
HOME
CHICKEN-POX.
ANOREXIA, DIARRHOEA, VOMITING.
"
CONSTIPATED
+ CURDS FROM 1 PINT MILK
R.H.S.C.
ANTUITRIN 1 C.c. DAILY (3 WKS.)
+ RADIOSTOL mv DAILY.
MARMITE ʒiii "
C.B., DRUMCHAPEL.
DIARRHOEA, VOMITING.
3 YRS.
MARMITE OMITTED
RADIOSTOL PELLETS IN PLACE OF DROPS (2, DAILY)
MUCH IMPROVED.
CORNFLAKES, SCRAPED BEEF SANDWICH
2 YRS.
NORMAL GAIN IN HEIGHT. [HOLT'S TABLES]
BEGINNING TO WALK AND SPEAK
(FONTANELLE CLOSED)
SECONDARY ANAEMIA
UPPER RESPIR. INFECTION.
(ANOREXIA, HORDEOLUM)
R.H.S.C.
Fe et Amm. Cit. q/ XV, CaSO4 ℞ 1/500 t.i.d.
OMIT IRON.
RABBIT, CHICKEN, or FISH.
3 BANANAS, DAILY.
PORRIDGE, ORANGE JUICE.
NORMAL GAIN IN WT. [HOLT'S TABLES]
AT HOME
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
WALKING WELL.
GOOD APPETITE.
MOTIONS PALE, FORMED.
OMIT PORRIDGE
ADD WHITE OF EGG.
SKIM. MILK, 3 PINTS DAILY.
LOOKING WELL
MOTIONS PALE, OFFENSIVE, BULKY.
GENU VALGUM.
4 YRS.
RADIOSTOL PELLETS, 4 DAILY.
4 YRS.

CASE VII.

Name:	Jean Wilkie.
Age;	$1^{9}/12$ years.
Admitted:	14/4/32.
Social Conditions:	Good.
Family History:	Father and mother healthy. Third child. Other two alive and well.
Previous History:	Full time normal labour. Apparently healthy at birth (Weight ? 12 lbs). Breast fed for 3 months then given Sister Laura's food till 9 months and throve well. Cut first tooth at 4 months. Began to walk at 10 months.
History of Illness:	From 16 months child had alternating attacks of diarrhoea and constipation. Six weeks before admission she was in bed for one week with a cough and from that time she refused to walk. The limbs became wasted. At the same time she became sulky and irritable. The appetite remained good.
Condition on Admission:	A pale 'pasty' child with a well-nourished face and body but wasted hypotonic limbs. Unable to stand. Irritable. She was 81 per cent. of her expected weight and 97 per cent. of her expected height. Anterior fontanelle patent. Teeth good.
	Abdomen - prominent. Motions pale and offensive.
	Heart, lungs, urine - no abnormality.
	Nervous System - knee jerks absent.
	Tuberculin Skin Tests (Mantoux and Pirquet) - negative.
	X-ray wrist - no rickets.

SPECIAL/

CASE VII (contd.).

SPECIAL INVESTIGATIONS:

Blood Pressure:	Systolic 64 mm. Hg. (26/5/33). 86 mm. Hg. (30/8/33).
Blood (10/6/33):	R.B.C. 4,520,000 per c.mm. W.B.C. 8,100 " " Hb. 60% Ring-staining of red cells.
(30/8/33): After iron treatment.	R.B.C. 5,300,000 per c.mm. W.B.C. 12,200 " " Hb. 74%
Biochemical Tests:	See 'J.W.' in Sections II-V.

Course of Illness:

14/4/32-22/4/32:	R.H.S.C.	With a diet of milk, porridge and pudding the motions remained pale, offensive and constipated. The right ear discharged for 4 days.
22/4/32-5/8/32:	Country Branch, Drumchapel.	During the first month she gained weight, then the appetite became capricious (She preferred bread to porridge). She remained irritable and could not be persuaded to walk.
5/8/32-16/9/32:	R.H.S.C.	For metabolism purposes she was given a diet of milk and sugar and during this time she lost weight. On 24/8/32 a coeliac dietary was commenced: sweet curd mixture 2½ pints, curds from 1 pink milk and 2 bananas daily. One week later blood and mucus were seen in the motions. Bacteriological examination revealed a dysentery bacillus (B. Flexner-Y). With Mag. Sulph. treatment the infection cleared up in a week.
16/9/32-26/5/33:	Country Branch, Drumchapel.	For two months the motions were constipated and she suffered from slight rectal prolapse. In spite of this she started to gain weight. Two/

CASE VII (contd.).

		Two scraped beef sandwiches and Radiostol m. iv daily were added to the diet. At the end of February 1933 she was walking well; the motions were large, offensive and contained black specks. These specks were seen to disappear on omission of banana. On 17/4/33 she was given skimmed milk in place of sweet curd mixture. During her 8 months' residence she gained 9 lbs. in weight and added 1 cm. to her height. She looked well and sunburnt and was of a brighter nature though still 'moody' at times.
26/5/33- 20/6/33.	R.H.S.C.	Cornflakes and orange juice were added to the diet. Blood examination revealed a secondary anaemia in spite of her good colour so she was given a two weeks' course of iron (Fe et Ammon. Cit. gr xv, $CuSO_4$ gr. 1/100 t.i.d.). Motions were large, pale, constipated, and numbered one to two daily.
20/6/33 onwards.	At home.	Her appetite remained good during the next 5 months, but her weight remained stationary. In October she had an attack of bronchitis with fever, which kept her indoors for two weeks. Her coeliac condition seemed little disturbed by it and her milk ration was increased to 3 pints daily; rabbit, porridge and an occasional tea-biscuit were also allowed. Radiostol pellets, 2 daily, were given in place of drops. At the age of 3 years she was still 81 per cent. of her expected weight and only 92 per cent. of her expected height. Apart from an attack of bronchitis in February 1934, which was accompanied by some loss of weight, the child showed a steady improvement in her weight chart. Growth in height was not marked, yet in the 9 months ending March 1934 she had gained 1 inch. Appetite was good and such articles/

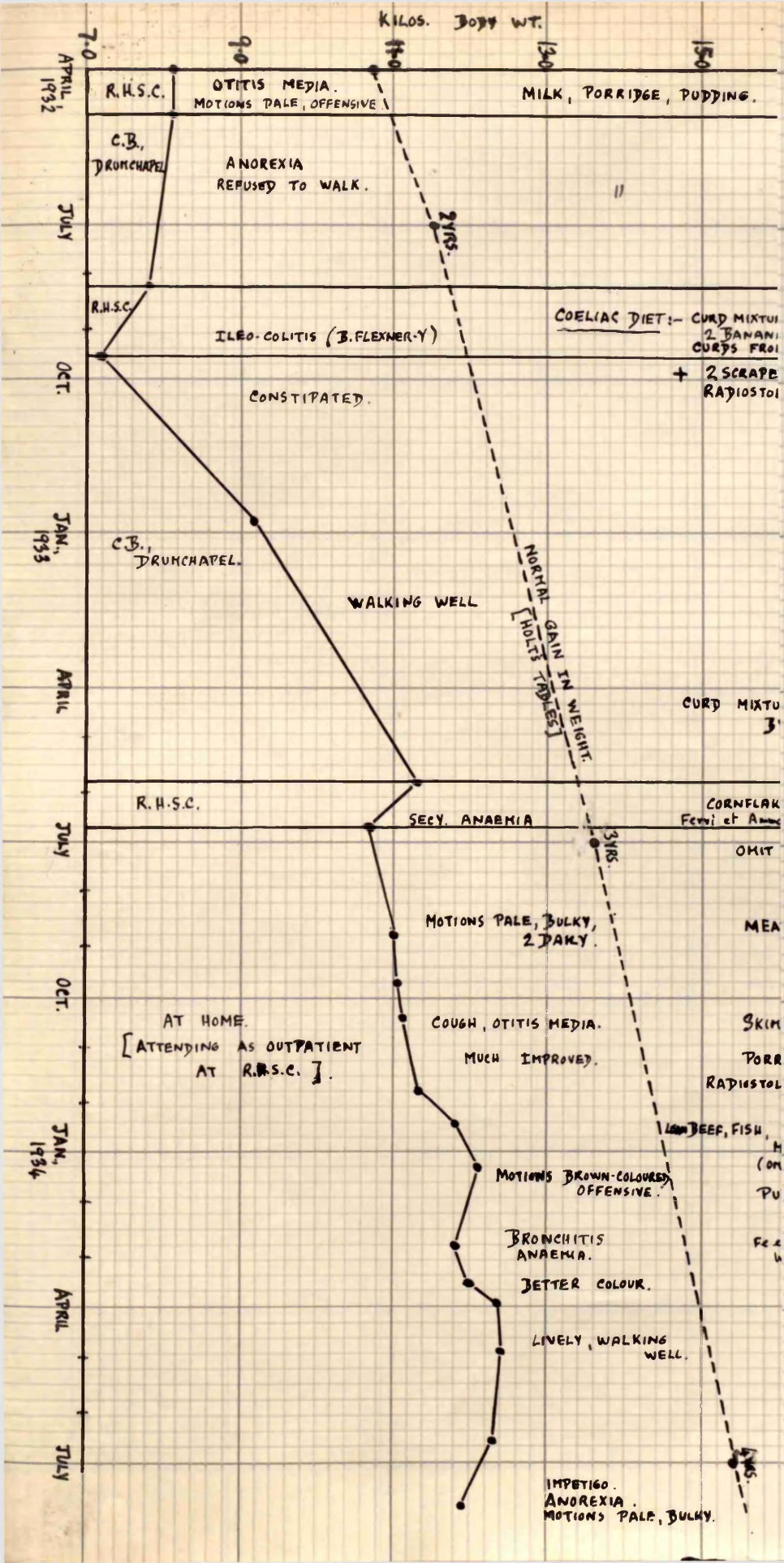
CASE VII (contd.).

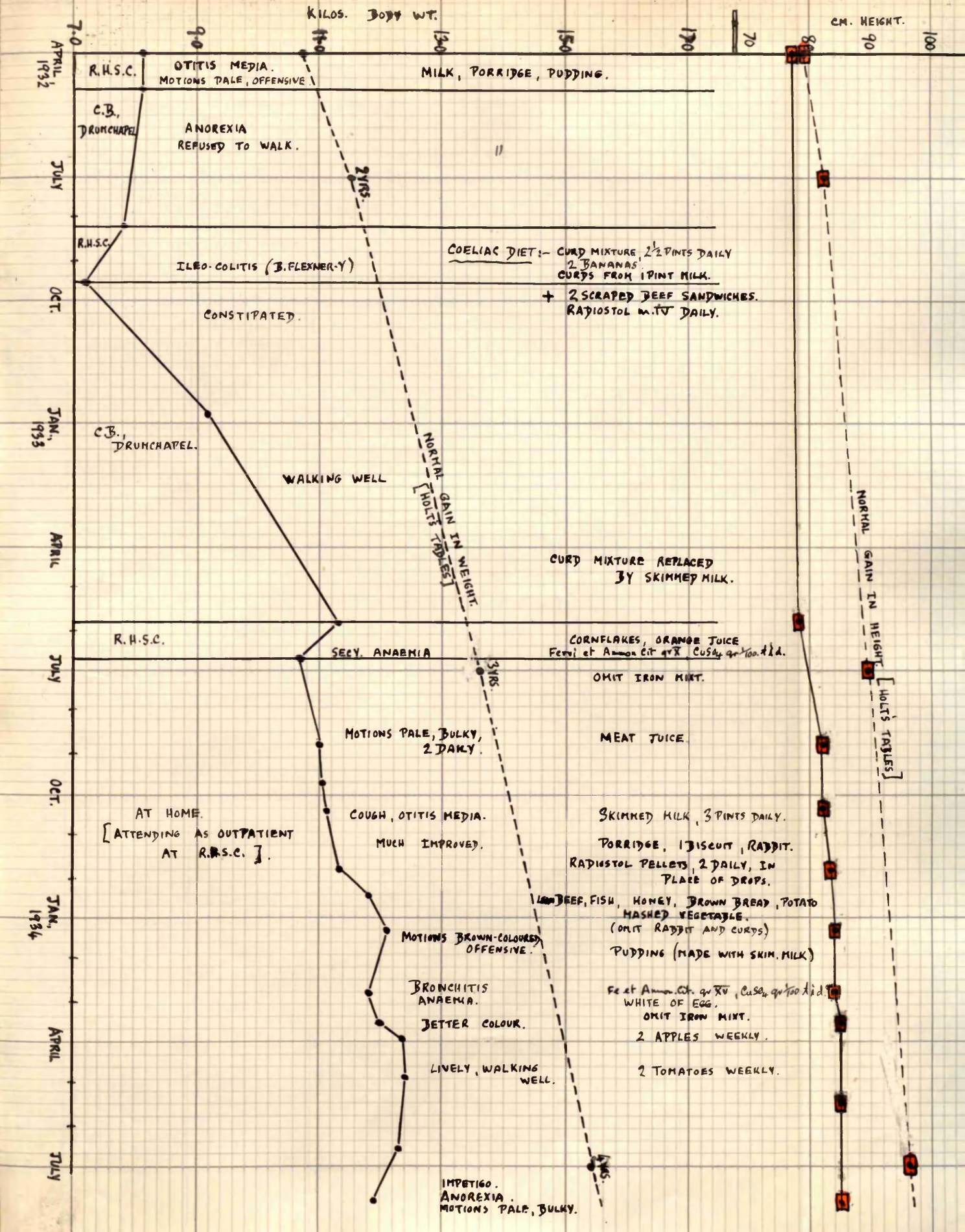
articles of diet as fish, mashed vegetable, apple, tomato, honey, brown bread, white of egg and puddings made with skimmed milk were introduced. At the end of February 1934 she was very pale and the heart revealed a basal systolic murmur; accordingly, a course of iron was given. Her hair was scanty and of fine texture, showing little tendency to grow.
X-ray of wrist on 29/3/34 showed 'tree-rings' but no rickets.
The motions became more normal in colour though sometimes offensive.

Condition on 25/9/34 (aet. $4^{3}/12$ years):

Child looked pale and had impetigo of face. She had not taken her diet well in the last 3 weeks and was 14 oz. less than in June 1934. She was now only 72 per cent. of her expected weight and only 86 per cent. of her expected height.

SEE CHART - next page.


KILOS. BODY WT.
7·0
9·0
110
130
150
APRIL 1932
JULY
OCT.
JAN. 1933
APRIL
JULY
OCT.
JAN. 1934
APRIL
JULY
R.H.S.C.
OTITIS MEDIA.
MOTIONS PALE, OFFENSIVE.
MILK, PORRIDGE, PUDDING.
C.B., DRUMCHAPEL
ANOREXIA
REFUSED TO WALK.
2 YRS.
R.H.S.C.
ILEO-COLITIS (B. FLEXNER-Y)
COELIAC DIET:- CURD MIXTU
2 BANANA
CURDS FRO
+ 2 SCRAPE
RADIOSTOL
CONSTIPATED.
C.B., DRUMCHAPEL.
WALKING WELL
NORMAL GAIN IN WEIGHT. [HOLT'S TABLES]
CURD MIXTU
3'
R.H.S.C.
SECY. ANAEMIA
CORNFLAK
Ferri et Am
3 YRS.
OMIT
MOTIONS PALE, BULKY, 2 DAILY.
MEA
AT HOME.
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
COUGH, OTITIS MEDIA.
MUCH IMPROVED.
SKIM
PORR
RADIOSTOL
BEEF, FISH,
MOTIONS BROWN-COLOURED OFFENSIVE.
PU
BRONCHITIS
ANAEMIA.
BETTER COLOUR.
LIVELY, WALKING WELL.
4 YRS.
IMPETIGO.
ANOREXIA.
MOTIONS PALE, BULKY.


KILOS. BODY WT.
7·0
9·0
110
130
150
170
CM. HEIGHT.
70
80
90
100
APRIL, 1932
JULY
OCT.
JAN., 1933
APRIL
JULY
OCT.
JAN., 1934
APRIL
JULY
R.H.S.C.
OTITIS MEDIA.
MOTIONS PALE, OFFENSIVE.
MILK, PORRIDGE, PUDDING.
C.B., DRUMCHAPEL
ANOREXIA
REFUSED TO WALK.
2 YRS.
R.H.S.C.
ILEO-COLITIS (B. FLEXNER-Y)
COELIAC DIET:- CURD MIXTURE 2½ PINTS DAILY
2 BANANAS
CURDS FROM 1 PINT MILK.
+ 2 SCRAPED BEEF SANDWICHES.
RADIOSTOL m.IV DAILY.
CONSTIPATED.
C.B., DRUMCHAPEL.
WALKING WELL
NORMAL GAIN IN WEIGHT [HOLT'S TABLES]
CURD MIXTURE REPLACED BY SKIMMED MILK.
R.H.S.C.
SECY. ANAEMIA
CORNFLAKES, ORANGE JUICE
Ferri et Ammon. Cit. gr X, CuSO4 gr 1/100. t.i.d.
3 YRS.
OMIT IRON MIXT.
MOTIONS PALE, BULKY, 2 DAILY.
MEAT JUICE
AT HOME.
[ATTENDING AS OUTPATIENT AT R.H.S.C.]
COUGH, OTITIS MEDIA.
MUCH IMPROVED.
SKIMMED MILK, 3 PINTS DAILY.
PORRIDGE, 1 BISCUIT, RABBIT.
RADIOSTOL PELLETS, 2 DAILY, IN PLACE OF DROPS.
BEEF, FISH, HONEY, BROWN BREAD, POTATO
MASHED VEGETABLE.
(OMIT RABBIT AND CURDS)
MOTIONS BROWN-COLOURED OFFENSIVE.
PUDDING (MADE WITH SKIM. MILK)
BRONCHITIS
ANAEMIA.
Fe et Ammon. Cit. gr XV, CuSO4 gr 1/100 t.i.d.
WHITE OF EGG.
OMIT IRON MIXT.
BETTER COLOUR.
2 APPLES WEEKLY.
LIVELY, WALKING WELL.
2 TOMATOES WEEKLY.
4 YRS.
IMPETIGO.
ANOREXIA.
MOTIONS PALE, BULKY.
NORMAL GAIN IN HEIGHT [HOLT'S TABLES]

CASE VIII.

Name:	Henrietta Baird.
Age:	2 years.
Admitted:	1/8/31.
Social Conditions:	Poor.
Family History:	Nothing of note.
Previous History:	Apparently healthy at birth. Breast fed 2 weeks then given Sister Laura's food till 4 months. Did not thrive and from 4 months till 6 months she had Mellin's food with cream of cow's milk. Thereafter she was given diluted cow's milk and oat-flour. Cut her first tooth at 10 months and was walking at 14 months. Beginning to talk at the time of admission.
History of Illness:	From $1^{6}/12$ years child had periodic attacks of vomiting, and anorexia accompanied by bulky stools. She became listless, irritable and disinclined to play or walk.
Condition on Admission:	A pale, dwarfed child, 72 per cent. of her expected weight. Tonsils enlarged. Abdomen: distended and doughy. Heart, lungs, nervous system - no abnormality. Tuberculin Skin Tests (Mantoux and Pirquet) - negative. X-ray wrist: No rickets. Leucocytes - 7,540 per c.mm.
Course of Illness:	After 2 weeks in R.H.S.C. the child was sent to the Country Branch, Drumchapel, for two months. Her condition/

CASE VIII (contd.).

condition did not improve and she was re-admitted to R.H.S.C. On 24/11/31 she had diarrhoea, she was pale and thin and showed signs of rickets. One week later she had improved and was dismissed home on 1/12/31 with instructions to attend the hospital at intervals.

On 21/1/32 she reported and her condition had not improved. She was now, at the age of 2 4/12 years, 64 per cent. of her expected weight. Stools were pale and bulky.

From 18/7/32 till 28/2/34 the mother failed to attend regularly with the child. In June 1933 tetany developed. Treatment with adexolin, marmite and iron was successful but there was a recurrence of tetany on 28/2/34 and she was readmitted to R.H.S.C.

Now at the age of 4½ years she was extremely emaciated and dwarfed, being as low as 43 per cent. of her expected weight and 82 per cent. of her expected height. There was carpal spasm and Chvostek's and Trousseau's signs were positive. X-ray of wrist revealed marked rickets and delayed ossification. The abdomen was distended.
Blood examination showed R.B.C. 2,930,000 per c.mm., W.B.C. 8,400 per c.mm., and Hb. 35 per cent.

She was given a diet of unskimmed milk and egg yolk.
On 7/3/34 urobilin was found in the urine. With the exception of the first two weeks in April 1934 the patient was given daily injections of antuitrin 1 c.cm. from 7/3/34 till 2/6/34. The fat metabolism was estimated after 2 weeks' and then after 6 weeks' antuitrin treatment and it was shown that fat absorption had increased by 6.5 per cent. on the first occasion and a further 1.7 per cent. on the second. The stools improved and from 12/4/34 till 2/6/34 an increase of almost 4 lbs. in weight was recorded.

Patient/

CASE VIII (contd.).

Patient was dismissed home on 14/6/34, and has reported at 3-4 weeks' intervals since.

At the age of 5 years in August 1934 she was still only 46 per cent. of her expected weight and 80 per cent. of her expected height. Motions were inclined to be loose. Six weeks later she was beginning to improve in general health and had risen to 54 per cent. of her expected weight.

CASES OF MALNUTRITION AND/OR GASTRO-ENTERITIS.

P.McK., male, 4/12. Birth 2 weeks premature. Breast-fed but mother had insufficient milk; one feed daily of cow's milk ℥ iv with Farola ℥ i added. On admission to hospital, baby only 66 per cent. of expected weight but did not look ill. Low-grade fever and loose stools for a few days. Breast-feeding attempted but not sufficient. Given sweet curd mixture then whole milk. Dismissed well.
(At time of blood sugar curve, 61 per cent. expected weight; motions loose, 3 daily; no fever; on whole milk diet).

M.T., female, 2/12. Normal full time labour. Breast-fed but did not appear to be thriving. Loose motions and occasional vomiting for 2 weeks. On admission to hospital, baby 64 per cent. of expected weight. Motions loose. Breast-feeding + supplementary feeds tried but former insufficient. Did well with cow's milk.
(At time of blood sugar curve, 64 per cent. expected weight; motions loose and greenish, 3 daily; on breast + supplementary feed).

W.R., male, 3½/12. Normal full time labour. Operation for pyloric stenosis at 3 weeks. Did well. Readmitted at 2/12 because of vomiting. Rapidly recovered with milk and sugar feeds. Loss of weight, diarrhoea and vomiting again at 3/12. On admission to hospital, baby 64 per cent. expected weight. X-ray with Barium revealed normal emptying of stomach. Vomiting at infrequent intervals continued for some days. Dismissed well.
(At time of curve, 61 per cent. expected weight, motions good; on diet of cow's milk and sugar).

H.I., male, 3/12. Birth 2 weeks premature (instrumental). Small baby. Breast fed 6 weeks but did not thrive. Nestle's milk given then later Sister Laura's food without improvement. Vomiting troublesome. On admission to hospital, 68 per cent. expected weight. Had upper respiratory infection for 10 days, then improved.
(At time of curve, 65 per cent. expected weight; motions 2 daily; not keen on feeds; on diet of milk and sugar).
Developed terminal broncho-pneumonia at end of 1 month.

C.C., female, 4/12. Normal birth. Twin, small baby. Berina food till 5 weeks. Did not thrive. Sister Laura's food tried but no improvement. Finally given diluted cow's milk. Diarrhoea and vomiting with convulsions. On admission to hospital, only 44 per cent. expected weight, dehydrated. Vomiting continued for 1 week then improved. (At time of curve, 44 per cent. expected weight; motions good, 2 daily: vomiting occasionally. On milk and sugar diet).
Afterwards developed broncho-pneumonia.

D.McV., male, 3/12. Birth 1 month premature. Bottle-fed (cow's milk and sugar in sufficient amount) and throve well till 3 days before admission when diarrhoea and vomiting commenced. On admission, 68 per cent. expected weight, secondary anaemia. Relapsed after getting on well. (At time of curve, 66 per cent. expected weight: motions loose but not frequent; on whole milkdiet.)

M.S., 18/12. Required resuscitation at birth. Breast-fed 6 weeks then given cow's milk and oatflour. Pneumonia at 6/52, followed by abscess of thigh. On recovery, developed a second attack of pneumonia (in hospital 5 weeks). Intermittent diarrhoea from 14/12.
On admission to hospital 100 per cent. expected weight. (At time of blood-sugar curve, 2-4 loose motions daily; on whole milk diet).

CRETINS.

J.H., female, 5/12 years: admitted 17/1/34.
Healthy at birth. Breast fed fourteen days then given cow's milk and sugar and appeared to thrive well. Shortly after birth, snuffles commenced (not haemorrhagic).
On admission, seen to have typical cretinoid facies - wrinkled brow, squat appearance, scanty, brittle hair, thick neck, widely patent fontanelles and sutures, nasal discharge, protruding tongue. Unable to support head for more than a few seconds.
X-ray wrist showed no ossification centres and a dense line at end of diaphysis.
Improvement noted at the end of 5 weeks on thyroid gr. ½ t.i.d.

E.C., female, 4/12 years: admitted 2/3/34.
Healthy at birth. Rhinitis since a few days old. At 3/12 skin became thicker and face changed. Child became apathetic and lost weight.
On admission, seen to have facial appearance of a cretin with open mouth and large tongue; breathing noisy, rubbery lax skin, wide fontanelle; also Mongolian eyes and thick head of coarse hair; bowing of tibiae. Given thyroid gr. ½ b.i.d.

I.G., female, 4 years; admitted 12/6/33.
Healthy at birth. Breast-fed and appeared to thrive till she took bronchitis at 9/12. Apathetic. Did not walk till 2 years. Not able to talk properly. Constipated.
On admission - a fat, flabby child, mentally dull and with a cretinoid facies: limbs very short; tongue large; skin coarse; X-ray wrist showed delayed ossification. After 5 months on thyroid gr. ½ 3 x general condition improved and said to be mentally brighter.

R.S., male, 3^{10}/12 years: admitted 26/1/34.
Labour 1 month overdue. Apparently healthy at birth. Breast-fed 3/12 then given boiled cow's milk till 1 year. Cretinism first noticed by the family doctor at 7/12. Thyroid gr. iii daily given till 3^{3}/12 years. Growth ceased during next 6 months when he had no thyroid. On admission he was not noticeably defective mentally, but of a phlegmatic disposition; he was overheight and overweight; skin dry, short neck and limbs, pads of fat over clavicle. Ossification within normal limits. Given increasing doses of thyroid (up to 12 gr. daily).

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