STUDIES IN THE METABOLISM, DIAGNOSIS AND THERAPEUTICS OF RICKETS.

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The investigations about to be described were carried out during the past three years at the Department of Medical Paediatrics, University of Glasgow, and in the Biochemical Laboratory of the Royal Hospital for Sick Children, Glasgow. All the biochemical analyses were carried out by me with the exception of the determinations of blood CO_2 and faecal fat which were made by Dr. Noah Morris. I am deeply indebted to Professor Leonard Findlay for the keen interest which he has taken in the work and for his stimulating criticism. I must also thank Dr. Noah Morris for whose helpful advice and constant encouragement I am exceedingly grateful.

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INTRODUCTION.

When one considers the readiness with which mineral metabolism is influenced by changes in acid-base equilibrium it is a curious fact that there has been carried out no complete investigation of rickets from this point of view. During the last century a vague concept held sway which expressed itself in "the acid theory of rickets". In 1923 Pritchard (1) in a discussion of the pathogenesis of rickets, advanced it as his opinion that "the essential basis, or the causa vera, of rickets is most probably a relative excess of acid bodies produced in the system by a disproportion between the intake and the output of energy". His arguments are purely theoretical. The chief experimental evidence in support of this view has been the finding of an increased urinary output of ammonia. In an investigation of thirteen cases of rickets Hodgson (2) found an increased urinary acidity and an increased excretion of ammonia by the kidneys. Although Freudenberg and Györgyi (3) confirmed his findings regarding an increased output of ammonia they found that in some cases the urine was neutral or alkaline. Burgess and Osman (4) have also reported an increased output of NH_4 in the urine of three cases of rickets.

György[5] who is the most ardent exponent of the theory of increased acid formation in rickets has, along with Freudenberg, put forward a physico-chemical theory of normal calcification which involves the combination of calcium with protein, the calcium proteinate combining with phosphorus with the subsequent release of the protein and the deposition of calcium phosphate. He considers that this process of calcification is interfered with in rickets because of an increased acidity of the bone-forming tissues. There has, however, been no direct evidence of this. In 1927 Bosanyi[6] investigated the pH of rachitic and normal cartilage and found as the result of colorimetric estimations that the pH was higher in the former being 7.6 as compared with 7.2 to 7.0 in the latter.

In his well known work on mineral metabolism in rickets Schabad[7] pointed out that the decreased urinary excretion of lime and phosphorus which he found in the early stage of this disease was against the theory of increased acid production. Some recent investigations would appear to give some support to his opinion. As a result of experimental work in rats Zucker, Johnson and Barnett[8] came to the conclusion that rickets develops better under conditions rather the opposite of an acidosis. Marked rickets was induced in rats by

feeding them on a diet of flour, casein, calcium lactate, sodium chloride and a trace of ferric chloride. Rats fed on a similar diet with the substitution in equivalent quantities of calcium chloride for calcium lactate developed mild rickets as compared with the control animals. On the addition of 2% ammonium chloride to the diets of rats receiving calcium lactate no rickets occurred, whereas the addition of 2% sodium carbonate to a well balanced diet did cause marked rickets. In his recent work on the treatment of rickets with irradiated ergosterol Hess (9) found that when rickets was induced with a diet containing Ca:P in the ratio of 11.5 to 1 and an excess of base over acid of 520 c.c. 0.1N alkali, the administration of large doses of codliver oil, irradiated ergosterol, or exposure to ultra violet light was followed by no healing of the rachitic lesions. When calcium chloride was substituted for calcium carbonate in equimolar amounts, the administration of specific agents caused healing. One must, however, consider the possibility of local changes in the alimentary tract playing an important part in such experiments as those just described of Zucker, Johnson and Barnett and of Hess in which the nature of the diet was altered.

Not only is the underlying physio-chemical pathology of rickets unknown but controversy still exists as to the nature of the actual disturbances in mineral metabolism which are present in the disease. Telfer (10) in his investigation of calcium and phosphorus metabolism in rickets in 1926 described a low urinary output of lime and phosphorus in active rickets and an increase during healing thus conforming the earlier work of Schabad. György (11), however, in his recent review of rickets and tetany states that during active rickets the urinary calcium remains within normal limits whilst the urinary phosphorus may be normal or increased, and that during healing a slight increase in both may occur but this is not constant.

It is of importance to settle this problem of the change in urinary excretion of calcium because of the importance it may have in considering the evidence for any change in the acid-base equilibrium in rickets, the amount of urinary calcium being readily influenced by conditions of acidosis.

The present investigation was primarily undertaken with a view to studying the absorption of calcium from the intestine in active rickets, but this led to what proved the major part of the work, namely, a study in

the rachitic child of the changes in intermediate metabolism which have been made manifest by the differences in the reaction to acidosis of normal children and children suffering from rickets. In view, however, of the difference of opinion among previous workers as to the changes in the kidney excretion of calcium and phosphorus it was decided first of all to obtain studies of the mineral metabolism in rickets and to compare them with similar studies in health. The question of intestinal absorption in rickets was then investigated before proceeding to the study of the effect of artificially induced acidosis on the metabolism of the normal and rachitic child.

The work is divided into four sections.

Section I deals with the metabolism of calcium and phosphorus in rickets with special reference to urinary excretion.

In Section II an investigation of the intestinal absorption of calcium and phosphorus is described and work relating to alimentary changes in rickets is discussed.

Section III is divided into two parts. Part I describes the effect of artificially induced acidosis on the mineral metabolism of the normal child. Part II

is concerned with the influence of acidosis and of variations in the calcium intake on the intestinal excretion of calcium in the non-rachitic animal.

Section IV describes the results of artificially induced acidosis on children suffering from rickets.

An addendum deals with rickets from a more immediately practical aspect and is composed of 2 parts, the first being the description of an investigation into the most practical method of estimating the phase of the disease, and the second dealing with the relative value of different therapeutic agents in bringing about cure.

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SECTION I. Studies on the Mineral Metabolism of Normal and Rachitic Children with special Reference to the urinary Excretion of calcium and phosphorus.

The metabolic studies about to be described were carried out in two groups comprising thirteen children. The first group includes seven normal children whose ages varied from five months to eleven years. In the second group are six children; four of these were examples of infantile rickets and were aged from six months to two and a half years; the other two were older children, aged nine years and twelve years respectively, suffering from late rickets. (The case histories of the latter two are given in Part 2 of the addendum on page 85). X-ray photographs of the wrist were taken in the younger members of the normal group to confirm as far as possible the absence of rickets. In the rachitic children the progress of the disease was followed in radiograms. The diet throughout the period of the investigation was constant, consisting of cow's milk with sugar sufficient to satisfy the caloric requirements of each child. After at least three days on the arranged diet the urine and faeces were collected with the usual precautions for a period of seven days. Complete balance studies

TABLE 1. Showing intake, output and retention of CaO and P_2O_5 in health.

Case	Age.	Total Intake		Faecal Output		Urinary Output		Retention		Daily Ret. per kilo.	
		CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5
	years.	gm.		gm.		gm.		gm		gm	gm
J.S.	5/12	7.526	9.408	4.752	4.928	0.094	1.872	2.680	2.608	.086	.084
J.McN	2½	12.00	16.50	7.925	4.755	1.075	9.216	3.00	2.529	.042	.035
R.F.	5.	14.40	19.80	10.255	6.829	0.882	10.788	3.263	2.183	.039	.025.
J.C.	9.	20.16	27.72	14.983	14.390	1.521	9.464	3.66	3.87	.018	.019
N.M.	10.	19.6o	26.95	10.959	9.627	1.784	11.102	6.857	4.996	.033	.029
J.D.	11.	16.80	23.10	10.742	6.341	1.032	14.63	5.026	3.130	.039	.016
J.G.	11.	20.16	27.72	9.508	6.818	1.406	11.55	9.246	9.352	.050	.050

TABLE 11. Showing intake, output and retention of CaO and P_2O_5 in Rickets.

CASE	AGE years	Phase of Disease	Total Intake		Faecal Output		Urinary Output		Retention		Daily Retention per kilo.	
			CaO gm.	P_2O_5	CaO gm.	P_2O_5	CaO gm.	P_2O_5	CaO gm.	P_2O_5	CaO gm.	P_2O_5 gm.
D.B.	6/12	Active	11.157	15.592	9.047	8.293	.035	5.18	2.075	2.119	.042	.043
		Induced Healing	11.157	15.592	5.771	2.137	.155	9.42	5.231	4.035	.104	.080
R.M.	2 1/12	Active	8.208	10.80	6.915	5.301	.067	3.696	1.226	1.803	.030	.044
		Spontaneous healing	13.23	15.876	8.496	5.569	.224	5.680	4.51	4.627	.090	.093
J.P.	2 3/12	Active	11.76	16.17	9.753	10.721	.095	3.128	1.912	2.321	.039	.048
		Induced Healing	11.76	16.17	4.272	3.126	.084	5.609	7.404	7.435	.153	.156
D.D.	2 7/12	Active	16.632	21.672	14.286	13.823	.050	5.17	2.296	2.679	.039	.045
		Induced Healing	16.632	21.672	2.121	1.606	.083	7.595	14.428	12.471	.255	.220
D.M.	9	Active	16.80	23.10	17.293	12.006	.069	10.501	-0.56	+0.593	-.003	+.002
		Induced Healing	16.80	23.10	2.673	1.803	.103	9.995	14.024	11.302	.099	.080
M.O'N	12	Active	20.16	27.72	14.431	13.97	.288	9.603	5.441	4.15	.029	.022
		Induced Healing	20.16	27.72	4.753	4.332	1.32	9.469	14.087	13.919	.079	.078

TABLE III.

Retention of CaO and P_2O_5 in normal Children at different ages.

AGE.	Daily Retention in grams per Kilo Body Weight.				
	Findlay, Paton & Sharpe	Telfer		Present Series	
Years	CaO	CaO	P_2O_5	CaO	P_2O_5
5/12				.086	.084
7/12	.178	.055	.055		
8/12	.069	.098	.060		
9/12		.064	.065		
1		.124	.123		
2½	.03			.042	.035
4	.054				
5				.039	.026
8	.046				
9	.037 .039			.018	.019
10	.047			.033	.024
11				.050 .039	.050 .016

CHART I

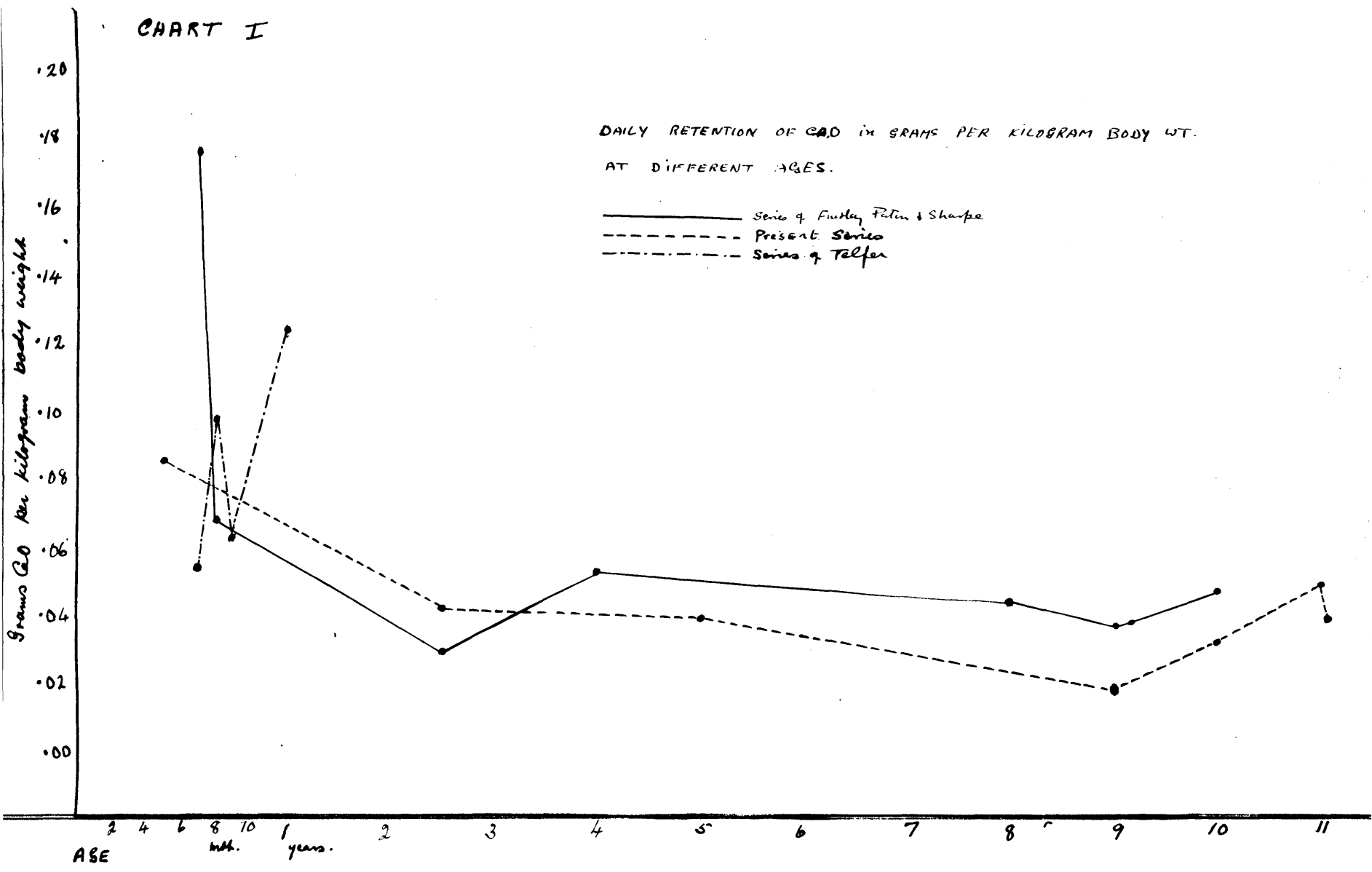

DAILY RETENTION OF CaO in GRAMS PER KILOGRAM BODY WT.
AT DIFFERENT AGES.
Series of Findlay Paton & Sharpe
Present Series
Series of Telfer
Grams CaO per kilogram body weight
·20
·18
·16
·14
·12
·10
·08
·06
·04
·02
·00
2 4 6 8 10 1 2 3 4 5 6 7 8 9 10 11
AGE
mth.
years.

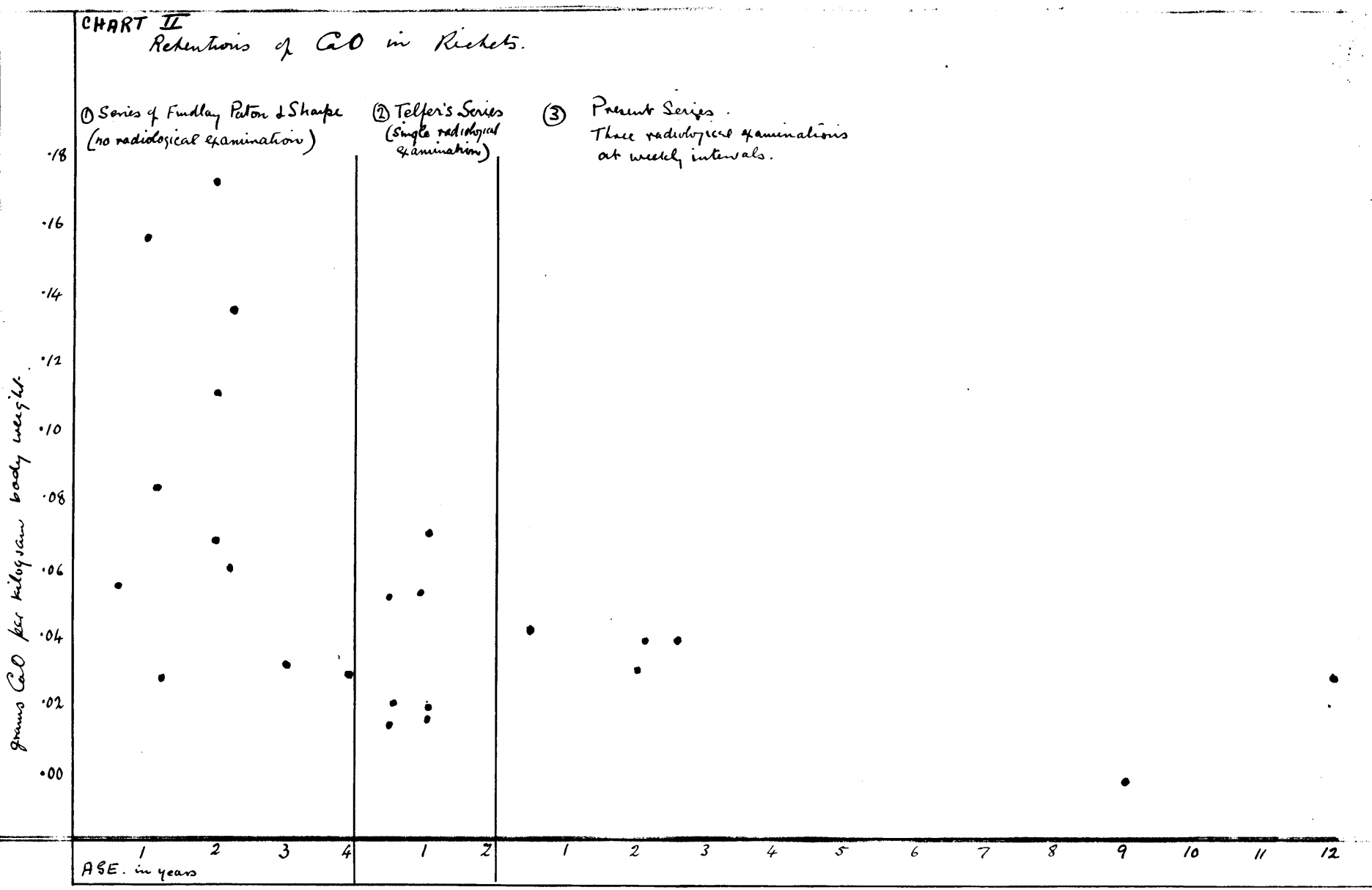
TABLE IV: Retentions of CaO & P_2O_5 in Rickets.

(1). Figures published by Findlay, Paton & Sharpe - as radiological evidence of phase of disease.
(2). Figures published by Telfer - single X-ray examinati
(3). Author's figures:- 3 weekly X-ray examinations.

Age yr.	Daily retention in grams per kilo. body weight. (1). F.P.S.	(2). Telfer		(3) Author.	
	CaO	CaO	P_2O_5	CaO	P_2O_5
6/12.		.052	.020	.042	.043
		.014	.016		
7/12.		.020	.015		
8/12.	.055				
11/12		.053	.065		
13/12.	.156				
		.016	-		
		.07	.08		
		.029	.019		
1.3/12.	.028				
	.082				
2.	.111				
	.067				
	.173				
2. 1/12				.030	.044
2. 2/12	.061			.039	.048
2. 3/12	.136				
2. 7/12				.039	.045
3.	.032				
4.	.029				
9.				-.003	.002
12.				.029	.022

CHART II

Retentions of CaO in Rickets.



were made in all the cases and the results are detailed in Table I (health) and Table II (rickets). The findings will be described under two headings, (1) Retention of CaO and P_2O_5 in health and in rickets, and (2) urinary excretion of CaO and P_2O_5 in health and in rickets.

(1) Retentions of CaO and P_2O_5 in health and in rickets.

The daily retention of lime in the normal children expressed in grams per kilogram body weight is given in Table III and Chart I along with similar figures published by Findlay, Paton and Sharpe [12] and by Telfer. [10] The method used by these workers is the same as the one used in the present investigation and their results provide an interesting comparison with those of the present series in that they confirm the variations met with at the different age periods, the relatively high retention per kilogram body weight in infants of 1 year and under, and the fairly constant retention per kilogram in children between the ages of 2 and 11 years.

The retention of lime in cases of rickets is shown in Table IV and Chart II which also include similar figures published by Findlay, Paton and Sharpe in 1921 and by Telfer in 1926. It will be noted how in the earlier work in which no radiological examinations

were made, the retention varied considerably in different cases. This was recognised by the authors to be due probably to differences in the phase of the disease. (See Part I of Addendum). In the later investigations of Telfer who made a single radiological examination in each case the retentions are not so varied. In the present series where the progress of the disease was followed in weekly radiograms for at least three weeks prior to the metabolic study the retentions are found to be positive (with one exception) but, on the whole, low. The chief points which arise in studying these retentions are -

(a) the influence of age on the retention of CaO and P_2O_5 per kilo. body weight in health, the retention of CaO varying between .05 and .12 grams in children of 1 year and under, and between .02 and .05 grams in children between the ages of 2 and 11 years.

(b) the presence of a positive though on the whole low balance of CaO in children suffering from active rickets.

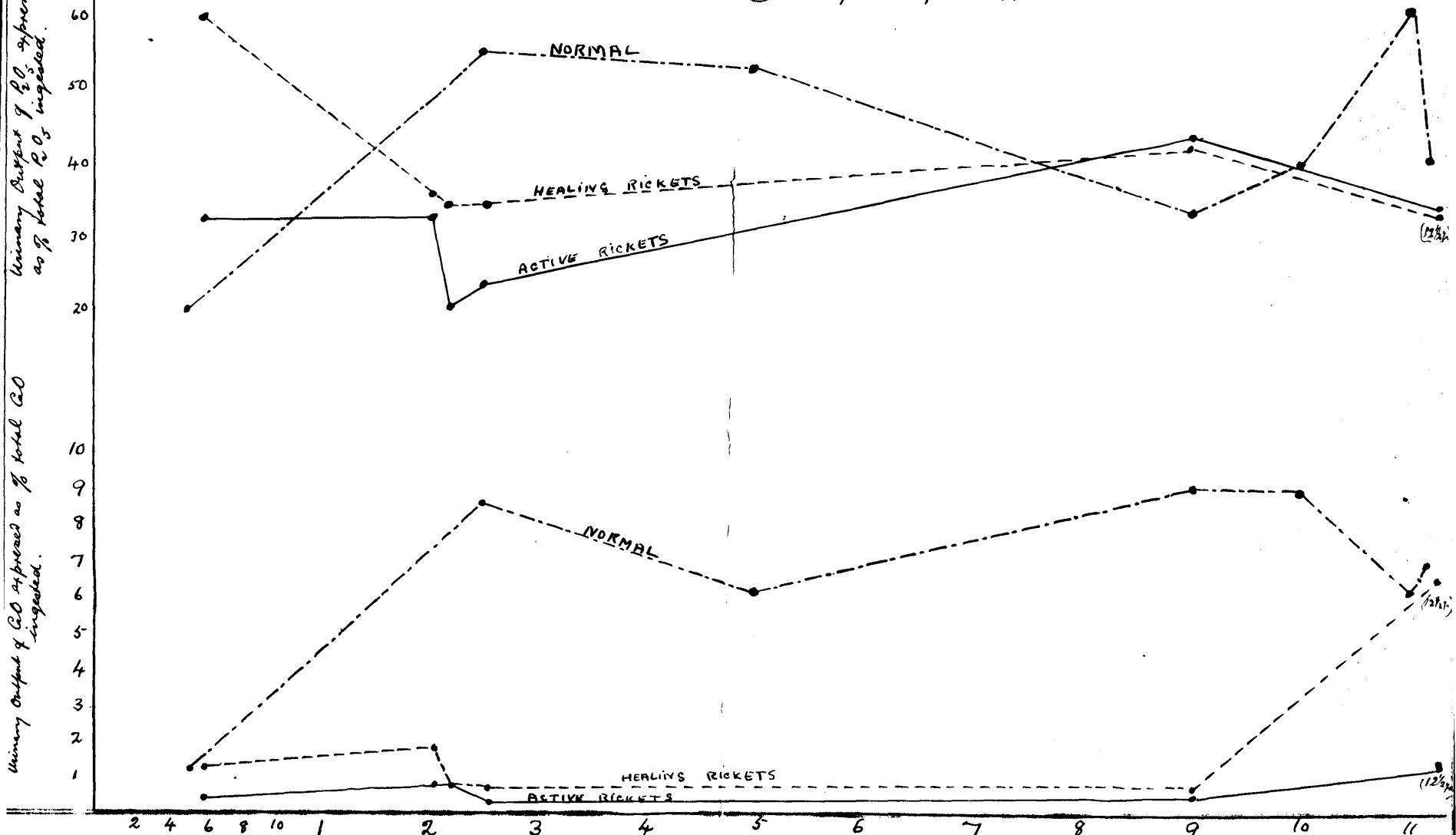
(2) Excretion of CaO and P_2O_5 by the kidney in health and in rickets.

Attention has been drawn by Györgyi to the fallacy of expressing urinary excretion of CaO in terms of percentage of total output. In active rickets the percentage of the total output of lime and phosphorus

TABLE V: Urinary output of CaO and P_2O_5 in normal cases and in rickets during the active and healing phases.

CASE	AGE yrs.	Weekly Output of CaO in grams.			Output of CaO as % of intake			Weekly output of P_2O_5 in grams			Output of P_2O_5 as % of intake		
		Normal Cases	Active Rickets	Healing Rickets	Normal Cases	Active Rickets	Healing Rickets	Normal Cases	Active Rick-ets,	Healing Rickets	Normal Cases	Act. Ric-kets	Healing Rickets
J.S.	5/12	.092			1.2			1.872			19.6		
D.B.	6/12		.035	.155		.31	1.38		5.18	9.42		33.0	60.1
R.M.	2 1/12		.067	.224		.80	1.7		3.696	5.68		34.0	36.4
J.P.	2 2/12		.095	.084		.80	.83		3.128	5.609		20.6	34.7
J McN	2 6/12	1.254			8.9			9.216			56.8		
D.D.	2 7/12		.050	.083		.29	.50		5.17	7.595		23.9	35.0
R.F.	5.	1.029			6.1			7.486			54.0		
J.C.	9.	1.521			9.2			9.464			34.0		
D.M.	9.		.069	.103		.42	.61		10.501	9.995		45.	43.
N.M.	10.	1.784			9.1			11.102			41.0		
J.D.	11.	1.037			6.1			14.630			63.0		
J.G.	11.	1.406			7.0			11.55			41.0		
M.O'N	12.		.288	1.32		1.4	6.6		9.603	9.469		34.6	34.0

CHART III Urinary output of CaO and P_2O_5 expressed as % of total CaO and % total P_2O_5 ingested in ① Normal Cases, ② cases of activ rickets and ③ cases of healing rickets.



found in the urine is of course less than normal because of the increased faecal output, and during the healing stage this percentage is increased because of the remarkable decrease which occurs in the faecal output during healing. The figures therefore, which are given in Table V represent actual quantities of CaO and P_2O_5 excreted by the urine over a period of one week. As, however, the age and weight of the children vary greatly excretion is also expressed as percentage of total intake which, as all the children were on a milk diet, is roughly proportionate to the age and weight of each child. The output expressed as percentage of intake is represented graphically in Chart III.

Results.

A. Urinary Excretion of CaO.

(a) Normal Cases: Just as a difference is noted in the retention of lime in children under 1 year sc a difference in urinary excretion of lime is found, this being markedly low in comparison with the excretion by the kidneys in children over the age of two years. In the present series of cases the weekly output of lime in the urine in the child under one year is .092 gm., representing 1.2% of the intake. This result is in accord with Telfer's findings in four children aged from

6 months to 8 months on a constant milk diet. In these infants the urinary excretion varied from 0.5% to 1.6% of the intake. The total weekly excretion in the seven children of the present series between the ages of 2½ and 11 years varies from 6.1% to 9.2% of the total lime ingested and shows no relationship to age.

(b) Rickets. In considering the urinary output of lime in cases of rickets it is important to keep in mind this marked change in urinary excretion which normally occurs between the ages of 1 and 2 years. Of the 6 cases of rickets only 1 is under 1 year, 3 cases are between 2 and 3 years and the other 2 are aged 9 and 12 years. In the case under 1 year the urinary output of lime during the active stage is below normal being 0.31% of the intake and during healing returns to about the normal figure of 1.38%. In the children between 2 and 3 years the urinary excretion is very much reduced during the active stage, varying from 0.29 to 0.80% of the intake. During healing the output is increased to from 0.5% to 1.7% of the intake, figures still much below the normal for children of that age. In the younger of the 2 cases of late rickets the urinary excretion, very low during the active phase,

has risen slightly during healing but has still remained much below the normal figure; in the other case the excretion has returned to within normal limits during healing.

B. Urinary Excretion of P_2O_5.

(a) Normal Cases: The urinary output of P_2O_5 is affected by age in a similar way to the urinary output of lime, but the change is not so striking or so constant. In the normal infant of 6 months 19% of the intake was excreted by the kidneys. It would seem, however, that there is a wide variation in the amount of P_2O_5 excreted in the urine of artificially fed infants. In Telfer's series of normal infants already referred to the amount excreted by the kidneys varied from 18% to 44%, the average being 33.7%. In the children of the present series between the ages of $2\frac{1}{2}$ and 11 years the figures are higher varying from 34 to 63% of the intake.

(b) Rickets: The case of rickets under 1 year excreted by the kidneys 33% of the total P_2O_5 ingested, and this was increased during the healing phase to 60%. The 3 rachitic children between 2 and 3 years excreted in the urine rather less than the normal amount namely from 20.6% to 34% of the intake. During healing the urinary excretion, 34.7% to 36.4%, approximated the

normal. The 2 cases of late rickets are different in that they show no reduction in urinary output of P_2O_5 during the active stage and no increase during healing.

Summary of Results.

These findings confirm the results of previous workers who found in active rickets a reduction in the urinary output of CaO and P_2O_5. During the healing phase the quantity of CaO found in the urine is, in most cases, only slightly raised and in no case is it increased above normal limits. This is in marked contrast to the supernormal retention of lime which occurs during healing. The changes found in the excretion of P_2O_5 by the kidneys are not so marked, the output being rather low during the active stage and about normal during healing.

Discussion: The cause of the diminished urinary output of CaO and P_2O_5 in active rickets may be either (1) an interference with absorption of CaO and P_2O_5 from the alimentary tract or (2) a change in endogenous metabolism possibly of the nature of an upset in acid-base equilibrium affecting excretion of lime and phosphorus by the kidneys. Many workers have considered that this decrease in urinary CaO and P_2O_5 associated with the increased

faecal output of these substances is indicative of defective absorption of either calcium or phosphorus from the alimentary tract although opinions differ as to which of these substances is primarily affected. Schabad suggested a primary disturbance in absorption of phosphorus which combined with calcium to form $Ca_3(PO_4)_2$ thus interfering with absorption of the latter element. He was led to this view because he found a greater faecal output of phosphorus than of calcium. Many American workers, notably Howland,[13] inclined to agree with this view and associated the defective absorption of phosphorus with the low inorganic phosphorus content of the blood. It would seen probable however that the low inorganic phosphorus content of the blood serum is due to some other cause than defective absorption. Zucker and Gutman[14] have shown that there is no decrease in the total phosphorus content of the blood in rickets but that the organic fraction is increased at the expense of the inorganic. Similar findings have led Bergeim[15] to suggest that there is a defect in the breakdown of organic phosphorus compounds.

In experiments on two cases of late rickets, Findlay and Telfer[16] showed that following a reduction in the intake of lime the faecal phosphorus decreased while the

urinary phosphorus was markedly increased to as much as 74% of the total output; on the addition of CaO to the diet a reduction in urinary phosphorus followed. From this they concluded that in rickets there is no primary defect in the ability of the intestine to absorb phosphorus. Murdoch (17) found that in rickets the ingestion of sodium dihydrogen phosphate was followed by a rise in the inorganic phosphorus content of the serum but with the subsequent simultaneous administration of NaH_2PO_4 and of calcium lactate, the level of the serum phosphorus fell. This phenomenon was also noted in normal children but the fall in the serum phosphorus was not so marked. This result was interpreted as indicating that in rickets there is a relative as well as an absolute excess of calcium in the gut owing to a primary defect in absorption of lime.

It would seem, in the light of Findlay and Telfer's evidence, that there is no primary interference in the intestinal absorption of phosphorus. There is, however, no conclusive evidence of any disturbance in the absorption of calcium. For this reason there was carried out the investigation of the intestinal absorption of calcium and phosphorus which is described in the next section.

The second explanation offered for the low urinary excretion of lime, namely a change in intermediate metabolism,

will be subsequently discussed in the section dealing with the influence of ammonium chloride on the metabolism of the rachitic child.

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SECTION II. The Absorption of Calcium and Phosphorus in Rickets.

I. The Absorption of Calcium.

Repeated analyses of the serum calcium following the ingestion of calcium salts have been made by several workers in studying the absorption of calcium both in the normal human subject and in animals, but have not previously been carried out in cases of rickets. Hjort,[18] compared the rise in serum calcium of normal dogs obtained after the ingestion of different salts of calcium including the lactate, chloride, glycerophosphate and carbonate. He obtained the highest rise with the use of the lactate and chloride, and the lowest with the glycerophosphate and carbonate,. After the administration of calcium lactate a maximum rise of from 17% to 48% occurred in 2 hours and the serum calcium did not quite return to normal till the end of 6 hours. The amount administered was 1.5 gm. per kilogram body weight and the method for determination of calcium in serum was that of Kramer and Tisdall.[19] Denis and Minot on the other hand found no rise in the serum calcium in normal human subjects after the oral administration of 6 gm. calcium lactate daily for a period of 10 days. Jansen[20] found that in man calcium bicarbonate was the

most reliable salt for producing an increase in serum calcium, calcium lactate being the least efficient. Varying results have also been reported by other workers. An average maximum rise of 80% was found by Kahn and Roe (21) in the normal human adult between the 6th and 7th hours after the ingestion of 5 gm. calcium lactate, the rise being maintained for 9 hours. Bauer and Ropes (22) obtained a maximum elevation of 14% and a minimum of 4% between the 1st and 4th hours after the administration of 5 gm. calcium lactate to the normal human adult, some elevation occurring over 12 hours.

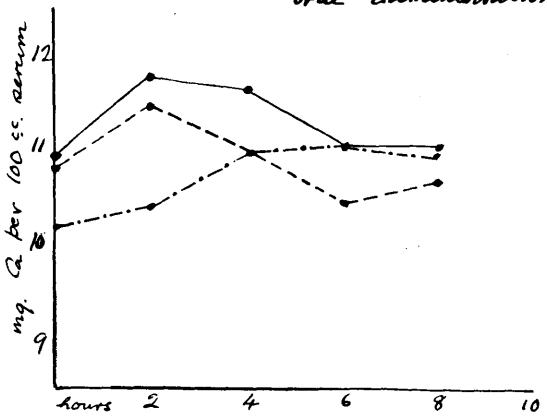
As these reports are so varied and as no results are available as to the effect of the ingestion of calcium salts on the serum calcium of normal children it was evident that before proceeding further a series of normal children must be studied. Accordingly calcium determinations were made on the serum of nine normal children before, and at two-hourly intervals after the ingestion of 4 gm. calcium lactate. The ages of the children varied from 4 months to 12 years. Similar experiments were carried out in 5 cases of active rickets uncomplicated by any clinical evidence of tetany and with a normal serum calcium; and in 6 cases of healing rickets.

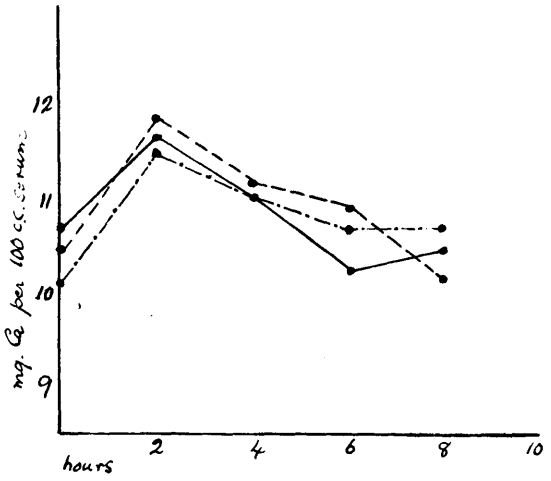
TABLE V1: The Calcium content of the serum in mg. per 100 c.c. in normal children before and after the oral administration of 4 gm. Calcium Lactate.

CASE	AGE YRS.	SERUM CALCIUM Before	2 hours after	4 hours after	6 hours after	8 hours after	Maximum Rise mg.	Maximum % Rise
J.N.	11.	10.91	11.81	11.72	11.00	11.18	0.90	8.2
A.U.	9/12.	10.70	11.50	10.88	10.32	10.96	0.80	7.4
W.C.	9.	10.32	10.41	10.87	11.15	11.05	0.83	8.0
K.D.	12.	10.78	11.61	10.81	11.18	10.45	0.83	8.0
A.M.	10½.	10.04	11.58	11.31	10.76	10.76	1.54	15.0
A.F.	4/12.	10.40	11.94	11.22	11.04	10.24	1.54	14.8
T.M.	7½.	10.13	10.45	11.22	11.04	10.95	1.09	10.8
J.M.	4.	10.82	11.38	10.94	10.69	--	0.56	4.8
K.G.	1.	9.91	10.90	10.99	10.45	10.18	1.08	10.8

AVERAGE RISE in mg.	1.02	AVERAGE PERCENTAGE RISE	9.7
MINIMUM " " "	0.56	MINIMUM " "	4.8
MAXIMUM " " "	1.54	MAXIMUM " "	15.0

CHART IV Normal Cases: Serum calcium before and after the oral administration of 4 gm. calcium lactate.





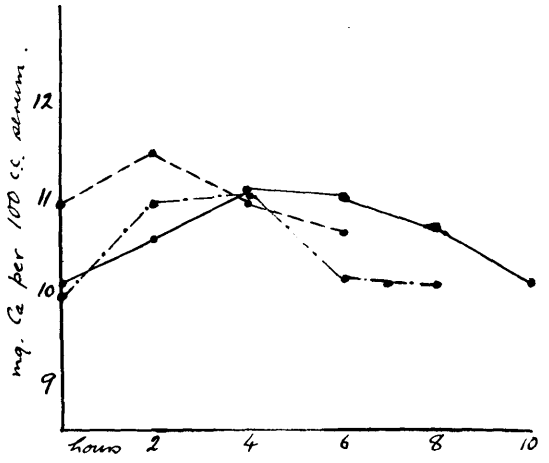
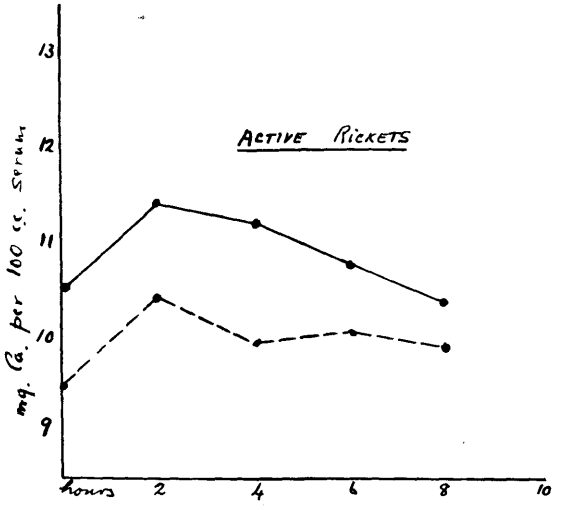


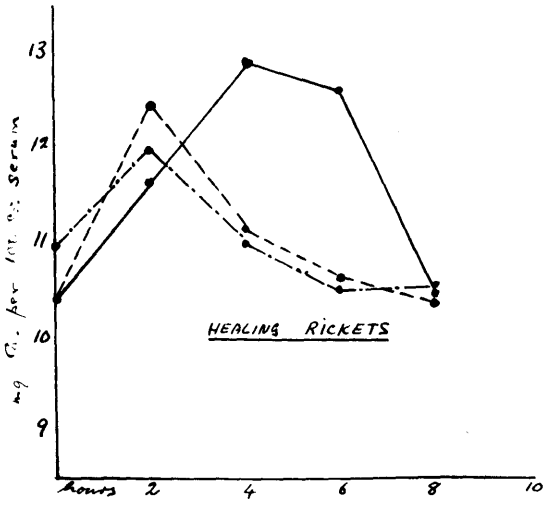
TABLE V11: Calcium content of serum in mg. per 100 c.c. in cases of active rickets before and after the oral administration of 4 gm. Calcium Lactate.

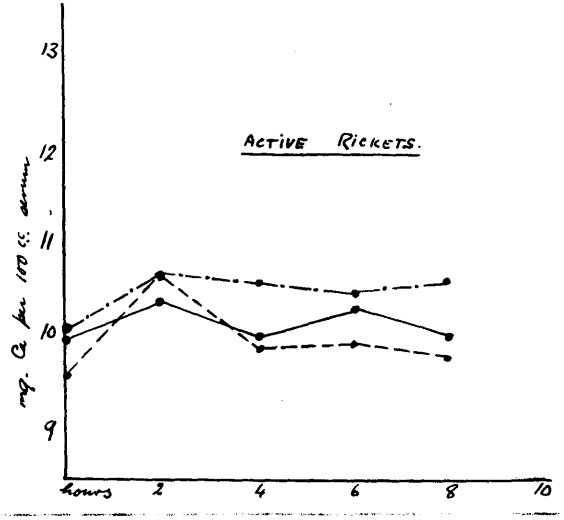
CASE	AGE.	SERUM CALCIUM Before	2 hours after	4 hours after	6 hours after	8 hours after	Maximum Rise mg.	Maximum % Rise.
R.C.	9/12.	9.73	10.38	9.82	10.38	9.91	0.65	6.6
W.K.	3 4/12.	10.04	10.76	9.77	9.86	9.68	0.72	7.1
M.L.	2.	9.56	10.60	10.52	10.47	10.64	1.08	11.3
E. B.	2.	10.55	11.46	11.28	10.73	10.36	0.91	8.6
D.M.	14/12.	9.49	10.50	9.77	10.13	9.77	1.01	10.6

AVERAGE RISE in mg.	0.87	AVERAGE PERCENTAGE RISE	8.84
MINIMUM " " "	0.65	MINIMUM " "	6.6
MAXIMUM " " "	1.08	MAXIMUM " "	11.3

CHART V : Serum Calcium after the oral administration of 4 gm. calcium lactate in active and healing rickets.







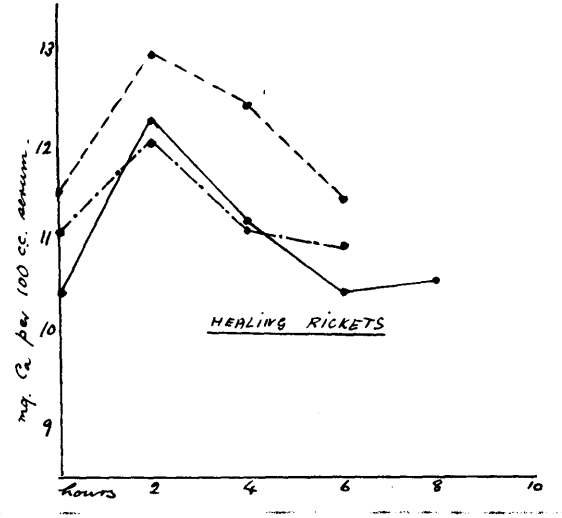


TABLE VIII: Calcium content of serum in mg. per 100 c.c. in cases of healing rickets before and after the oral administration of 4 gm. calcium lactate.

CASE.	Age.	SERUM CALCIUM Before	2 hours after	4 hours after	6 hours after	8 hours after	Maximum Rise mg	Maximum % rise
J.G.	5. yr.	10.30	11.63	12.94	12.68	10.48	2.64	25.6
M.C.	18/12.	10.47	12.47	11.14	10.66	10.47	2.0	19.1
M.L.	2.	10.84	11.90	10.95	10.50	10.50	1.06	9.8
E.B.	2.	10.37	12.31	11.29	10.37	10.64	1.94	18.7
D.D.	2.2/12.	11.58	12.80	12.40	11.40	--	1.22	10.5
D.M.	14/12.	11.03	12.01	11.13	10.73	--	1.58	8.8

AVERAGE RISE IN mg.	1.74	AVERAGE PERCENTAGE RISE	15.4
MINIMUM " " "	1.06	MINIMUM " "	8.8
MAXIMUM " " "	2.64	MAXIMUM " "	25.6

Results.

Normal Children: (Table VI and Chart IV).

In the majority of the normal children the maximum elevation occurred at the end of 2 hours and had returned to normal in 6 hours. In 3 cases, however, the maximum rise did not occur until 4 to 6 hours after administration of the salt and in 2 of these cases the serum calcium was still high at the end of 8 hours. The degree of increase varied greatly, the minimum being 4.8% or 0.56 mg. and the maximum 15% or 1.54 mg., while the average was 9.7% or 1.02 mg. The results show no relationship to age, the 2 greatest increases, namely 15% and 14.8% having occurred in children aged 10½ years and 4 months respectively, while the lowest rise of 4.8% occurred in a child of 4 years.

Active Rickets: (Table VII and Chart V).

In the cases of active rickets the type of curve resembles closely that met with in the normal, the maximum rise generally occurring at the end of 2 hours, and the degree of rise varying considerably in different cases - from 0.65 mg. or 6.6% to 1.08 mg. or 11.3%, the average rise being 0.87 mg. or 8.84%, a figure somewhat lower than the normal average.

Healing Rickets: (Table VIII and Chart V).

In the 6 cases of healing rickets the ingestion of

calcium lactate was followed in all cases by an increase in the serum calcium greater than the average increase in the normal group, and the average rise of 1.75 mg. or 15.4% was higher than the maximum for the normal group. These curves resembled the curves of the other groups in that the maximum rise was noted in 2 hours and had returned to normal in 6 hours, the one exception to this being Case I, J.G. where the maximum rise occurred in 4 hours and returned to normal in 8 hours.

Summary of Results.

In active rickets ingestion of a large quantity of calcium lactate is followed by a rise in the serum calcium to a degree slightly less than that which is found in the normal subject, while during the healing phase a supernormal rise occurs.

II. The Absorption of Phosphorus.

The absorption of phosphorus by the intestine has already been studied both in health and in rickets by means of repeated analyses of the inorganic phosphorus content of the serum after the oral administration of sodium phosphate. In 1925 Klercker and Odin (23) showed that the ingestion of a soluble phosphate was followed by a rise in the inorganic phosphorus of the serum.

Murdoch[17] in 1927 noted the effect of the ingestion of sodium dihydrogen phosphate on the inorganic phosphorus content of the serum in five normal children, in four children suffering from active rickets and in two in whom healing was in progress. In both the normal cases and cases of active rickets she obtained an average rise of 2.0 mg. per 100 c.c. at the end of 1-2 hours, and in the 2 cases of healing rickets increases of 5.1 mg. and 7.0 mg. respectively. In the following year Warkany[24] published the results of a similar series of experiments. In 3 normal cases he obtained a rise of from 2.4 to 4.5 mg. per 100 c.c. serum in 1 to 2 hours after the ingestion of 5 gm. disodium hydrogen phosphate, in 5 cases of active rickets a rise of from 0.1 mg. to 1.0 mg. per 100 c.c. serum after a dose varying between 2.5 and 4 gm. $Na_2H\ PO_4$, and in 5 cases of healing rickets a rise varying between 2.4 and 7.6 mg. per 100 c.c. serum. The results obtained in his cases of active rickets are strikingly different from those of Murdoch's series. It is to be noted however that Murdoch used an acid salt (NaH_2PO_4) while Warkany used an alkaline one ($Na_2H\ PO_4$). It was considered probable that this might be the explanation of the discrepancy in these two workers' results.

TABLE IX: Inorganic phosphorus in mg. per 100 c.c. serum in cases of active rickets before and after the oral administration of 4 gm. $Na\ H_2\ PO_4$ and 4 gms. $Na_2\ H\ PO_4$

Case	Age yr.	Serum Phosphorus before	1 hour after	2 hours after	4 hours after	Maximum rise mg.	REMARKS.
W.G.	1½	3.4	4.9	5.7	4.3	2.3	4 gm. NaH_2PO_4 per os
H.R.	2	2.4	6.3	5.5	4.4	3.9	do do
R.M.	2	3.2	6.4	7.2	4.1	4.0	4 gm. Na_2HPO_4 per os
J.M.	1	4.0	4.4	6.0	4.1	2.0	do do

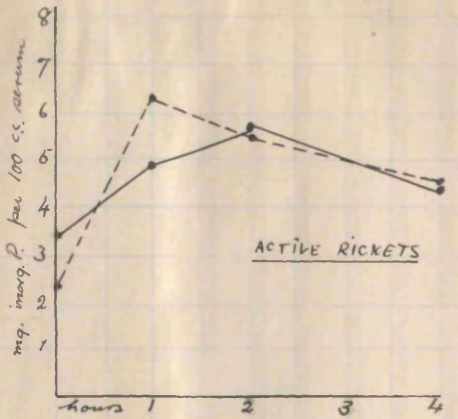
AVERAGE RISE AFTER $NaH_2\ PO_4$ 3.1 mg.
do do do Na_2HPO_4 3.0 "

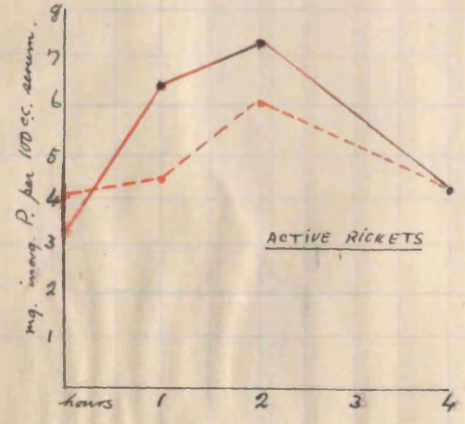
TABLE X: Inorganic phosphorus in mg. per 100 c.c. serum in cases of Healing rickets before and after the oral administration of 4 gm. NaH_2PO_4 and 4 gm. $Na_2H\ PO_4$

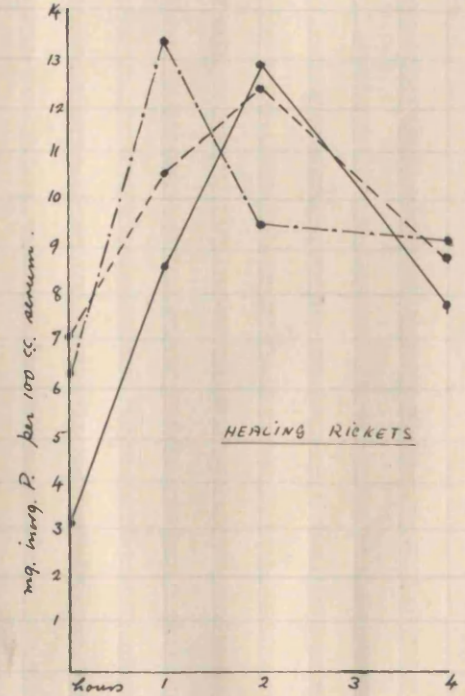
Case	Age yr.	Serum Phosphorus before	1 hour after	2 hours after	4 hours after	Maximum rise mg.	REMARKS.
R.K.	2	3.1	8.6	12.9	7.7	9.8	4 gm. NaH_2PO_4 per os
H.W.	1	7.0	10.6	12.4	8.8	5.4	do do
H.C.	2	6.3	13.3	9.5	9.2	7.0	do do
M.B.	1½	4.9	8.9	8.1	7.3	4.0	do do
B.M.	2½	6.1	12.9	9.4	6.9	6.8	do do
J.P.	2	3.6	8.0	8.5	5.7	4.9	4 gm. Na_2HPO4 per os

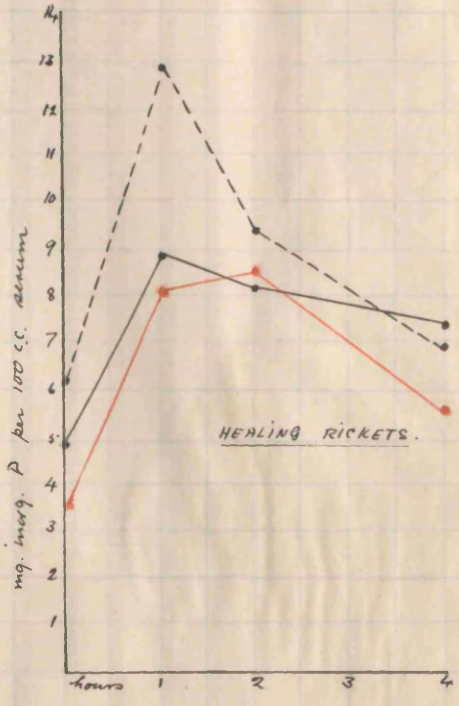
AVERAGE RISE AFTER $NaH_2\ PO_4$ 6.6 mg.
MINIMUM " " " " 4.0 "
MAXIMUM " " " " 9.8 "
RISE AFTER $Na_2\ HPO_4$ 4.9 "

CHART VI: Inorganic phosphorus content of the serum before and after the oral administration of NaH_2PO_4 (black lines) and of Na_2HPO_4 (red lines) in active and healing rickets.









Consequently in the present investigation both salts were used. Four cases of active rickets were studied, 2 of whom received sodium dihydrogen phosphate and 2 disodium hydrogen phosphate. Six cases of healing rickets were also investigated, 5 after the administration of NaH_2PO_4 and 1 after $Na2HPO_4$.

Results. (Tables IX and X and Chart VI).

In the 2 cases of active rickets who were given the acid salt the increases noted were respectively 2.3 mg. and 3.9 mg. per 100 c.c. serum, representing an average of 3.1 mg., while in the 2 cases given the alkaline salt the increases were respectively 2 mg. and 4 mg., or an average of 3.0 mg. The average rise over all the vases of healing rickets was 6.3 mg., the minimum being 4.0 mg. and the maximum 9.8 mg. A rise in the serum phosphorus of 4.9 mg. occurred in the case who received the alkaline salt.

These results confirm Murdoch's findings that in active rickets the rise in serum phosphorus following the oral administration of NaH_2PO_4 is similar to the rise obtained in health. A similar rise was noted following the administration of Na_2HPO_4. The increased rise in the phosphorus level noted by both Murdoch and Warkany during the healing phase of the disease is confirmed by the results obtained in the present series.

Discussion: The recognition of the importance of the pH of a solution in affecting the solubility of calcium, has led many workers to investigate the reaction of the gut in rickets. Until recently it was generally accepted that the only parts of the alimentary tract normally with an acid reaction were the stomach and the first part of the duodenum; the jejunum, ileum and large intestine being considered alkaline. According to this theory the area through which calcium could be absorbed was limited to the stomach and a very small part of the small intestine. MacClendon and others[25] however, in 1919 showed that the whole of the small intestine in pups, dogs and cats is on the acid side of neutrality, and a year later they[26] reported results showing that in man the duodenum and jejunum are normally acid. These results were confirmed in 1927 by Lloyd Arnold[27] in dogs. The importance of this observation with regard to the absorption of calcium is at once evident, absorption being possible over a much larger area than was formerly supposed. Investigations of the reaction of the gut in rachitic children have been limited to studies of gastric acidity and the reaction of the faeces. Wills, Sanderson and Paterson[28] found an increase in the degree of gastric acidity during healing rickets but they considered that such increase was related rather to improvement in general

well-being than to healing of the disease. Schloss[29] was the first to point out that in active rickets the faeces were alkaline while during healing the reaction tended to change to acid. More recently a study of the calcium and phosphorus content along with the pH values of the faeces was made by Redman[30] in rachitic children. He determined the pH value in fresh samples and the Ca and P content in dried samples of faeces from cases of active and healing rickets, and noted a certain correlation between the Ca and P content and the pH value confirming the previous work of Schloss.

Much work has been carried out in animals on the effect of the production of rickets and its subsequent healing on the reaction of the faeces. Zucker and Matzer[31] in 1923 showed that the faeces of albino rats are normally acid, and become alkaline on the production of rickets. On treatment of rachitic rats with cod-liver oil or ultra-violet light he found that a definite increase in acidity occurred. This work has subsequently been confirmed by Jephcott and Bacharach[32] and by Yoder[33] in rats, and by Redman, Willimot and Wokes[34] in guinea-pigs and rats.

Determinations of the pH values of the contents of the small and large intestine at different levels have also been made and in spite of the great technical

difficulties involved in this procedure the consistency of the results makes them worthy of consideration. Such experiments were carried out by Grayzel and Millar[35] in normal dogs, in dogs fed on a rickets-producing diet (Mellanby's diet), and in dogs fed on Mellanby's diet + codliver oil or exposure to ultra-violet light. The animals were killed 4 to 6 hours after feeding when it was considered intestinal digestion was at its height and no sharp cyclic change in reaction was occurring. The stomach, the intestine in two-foot lengths, the caecum and the colon were isolated and the pH determined, both electrometric and colorimetric methods being used. In normal dogs they found the reaction acid throughout the small intestine becoming slightly alkaline in the large. The reaction of the small intestine in the 6 rachitic dogs was to the alkaline side of neutrality while in the rachitic dogs treated with codliver oil or ultra-violet light the reaction was acid. In similar experiments on rats Tisdall and Price[36] found the acidity of the upper intestine of normal rats greater than that of rachitic rats while on the exposure of the rachitic animals to sunshine the reaction approximated the normal.

The consistency of these workers' results lends support to the theory that in rickets there is a change

in the intestinal pH to the alkaline side. On the ordinary milk diet of the infant containing as it does CaO and P_2O_5 in the approximate ratio of 1/1.38 it is easy to understand how an increased intestinal pH would lead to increased formation of insoluble $Ca_3(PO_4)_2$ and hence to some degree of disturbance of absorption of both these elements.

In the present experiments the only evidence we have of defective absorption is the slight flattening of the calcium curve in the cases of active rickets. This however may be explained not only as possibly due to a slower rate of absorption but also to an increased rate of excretion. If calcium is eliminated more quickly from the blood in rickets it must be excreted by the bowel as we know there is a diminished excretion by the kidney. We are thus brought to the problem of whether the increased faecal calcium is due to an interference with absorption or an increased excretion.

There are several points which may help in deciding which of these possibilities is the more probable - (1) the increased pH found experimentally in the intestine of rachitic animals rendering calcium salts more insoluble, (2) the fact that following a reduction in the intake of calcium in the diet the greater part of the phosphorus

becomes excreted by the kidneys and (3) the normal phosphorus curve considered along with the excess of both calcium and phosphorus found in the faeces of rachitic subjects. If this excess faecal output of Ca and P were due to an increased excretion of Ca and P. then we should expect a flattening of the serum P. curve similar to that of the calcium one because of an increased rate of elimination of phosphorus from the blood. We find, however, a normal serum P curve and Murdoch has shown that if calcium lactate be given along with phosphate the level of the serum phosphorus remains lower.

When these points are considered the evidence would seem to be in favour of an interference with absorption, the primary change probably being an increase in pH followed by an increased formation in the gut of $Ca_3(PO_4)_2$ thus leading to an interference in absorption of both calcium and phosphorus. But we must admit that such evidence as we have is by no means conclusive and we still lack an entirely satisfactory solution of the problem.

The issues are confused in that we do not yet know how much of the faecal calcium under normal conditions is excreted by the intestine, and how much is the unabsorbed residue of the intake. The investigation of the effect of ammonium chloride in normal children described in the

first part of the next section as well as providing a study of the reactions of the normal child to acidosis was undertaken with the hope of throwing some light on this problem, while the experimental work on pigs described in the second part of the next section was carried out with the elucidation of this problem as its chief aim.

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SECTION III. Part I. Metabolic Reactions of the Normal Child to acidosis induced by Ammonium Chloride.

Acidosis is so frequently put forward as the underlying pathological condition in such a variety of disorders that it is important to appreciate what actually are the metabolic manifestations of the acidotic state. Clinically one seldom, if ever, has an opportunity of studying acidosis uncomplicated by some such other factor as inanition or toxaemia. It is therefore advisable in an investigation of the metabolic reactions to a disturbance in acid-base equilibrium to have these secondary factors as far as possible excluded. This can only be done when the acidosis is induced in a healthy individual with the minimal amount of upset especially as regards food intake, and such a condition is most nearly attained in the acidosis produced by the ingestion of NH_4Cl. Haldane (37) was the first to show that NH_4Cl taken in large amounts led to a marked acidosis owing to its ammonium moiety being converted into urea. Since then many papers have been published dealing with the changes following the administration of this substance.

This investigation was undertaken with the object of studying the changes which occur normally in mineral

metabolism during acidosis and of comparing these changes with changes similarly induced in cases of rickets. The urinary excretion of chlorine, ammonia and titratable acid as well as changes in the chemical composition of the blood were also studied. Most workers are agreed that there is an incfeased output of lime in the urine during acidosis. The effect on the faecal excretion of lime and the influence of the acidotic state on the phosphorus metabolism have not however been previously determined. Steenbock, Nelson and Hart (38) have pointed out the detrimental effect of acid-forming diets on calcium retention and calcification in animals. Sawyer, Bauman and Stevens (39) found an increased urinary output of calcium and phosphorus in two children during a period of high fat intake: in only one, however, was there an increase in the faecal amounts of these substances, while in the other there was a decrease. In a study of acid and base-forming diets in adult women Bogert and Kirkpatrick (40) did not obtain a constant change in the amount of faecal calcium during the period of acid-forming diet although the urinary lime was always increased. In infants Flood (41) found that administration of N/10 HCl led to no alteration in the retention of calcium although this substance always

appeared in slightly increased amount in the urine.

The subjects of the present study were four apparently normal children - N.G. female aged 9 years; W.C. male aged 9 years- N.M. female aged 10 years; and J.F. male aged 9¼ years. Each had recovered from a mild attack of rheumatism. Balance studies were carried out in a similar way to those described in the first section. Thereafter 1 gram of ammonium chloride was administered 5 times daily in capsule form and balance studies again made. In the case of N.M. and J.F. the ammonium chloride was continued so as to include a third period of 5 and 6 days respectively. In the case of N.M. 1 drm. codliver oil was given 3 times daily during this last period.

Clinical features: No apparent change was produced in the appearance of any of the children during or following the ingestion of the ammonium chloride. In 2 cases the administration continued for a period of 18 days without any sign of circulatory disturbance. The daily intake varied from 0.166 to 0.247 grams per kilogram body weight. Haldane produced in himself marked respiratory distress by taking one dose of 25 grms. of ammonium chloride equivalent to 0.25 grams per kilogram body weight. Koehler (42) found that administration of 10-15 grams of ammonium chloride daily to well-developed adults

produced definite symptoms of listlessness, thirst, diuresis and muscular aches: these subjects, however, were all patients recovering or recovered from lead-poisoning. Three explanations may be offered for the difference between our results and the results recorded elsewhere. First, children may not be as susceptible as adults to the action of ammonium chloride. It is well known that children tolerate a much larger dose per kilogram body weight than adults of such a drug as Salvarsan. It seems strange, however, that this should be the case with an acid-producing substance when the peculiar susceptibility of the young to disturbances of acid-base equilibrium is remembered. Secondly, the difference in the diets of our subjects and those of the adults may be of importance since milk contains an excess of fixed base over mineral acid. It is possible that this excess base enabled our subjects to withstand the acidosis more effectively than would otherwise have been the case. Thirdly, the division of the daily dose into 5 portions may have allowed the compensatory reactions of the body to come into play before there was any necessity for visible extra effort on the part of the respiratory or other system. The last seems to be the most likely explanation: but whatever the cause may have been the absence of clinical manifestations of

TABLE Xl. Changes in Chemical Composition of Blood.

NAME	STAGE	(1) CO_2 Vol.%	(2) Calcium mg.%	(3) Phosphorus mg%
N.G.	Normal	55.1	-	-
	7 days NH_4Cl	38.7	-	-
W.C.	Normal	68.2	10.6	5.2
	4 days NH_4Cl.	41.4	-	-
	8 " "	40.3	10.1	6.5
J.F.	Normal	66.7	9.1	-
	9 days NH_4Cl.	49.1	9.1	-
	19 " "	45.8	8.80	-
N.M.	Normal	60.6	9.25	4.2
	3 days NH_4Cl	45.1	-	-
	6 " "	41.8	-	-
	9 " "	43.4	9.8	4.1
	13 " "	41.5	-	-

acidosis in no way invalidates this study for, as will be shown later, the blood analyses were indicative of a disturbance of the acid-base equilibrium towards the acid side. The principal object being to study the changes over a period of several days it would have been manifestly impossible to have accomplished this in the presence of respiratory distress or other evidence of acute acidosis.

Changes in Chemical Composition of the Blood:

A. Carbon dioxide (Table XI Column 1). The total CO_2 content of the blood was reduced in every case. Keith and Whelan (43) found that the plasma CO_2 dropped about the 4th or the 5th day of the administration of ammonium chloride. In the last three subjects the CO_2 content was estimated 2 or more times during the ammonium chloride period. From these results it is evident that the reduction in the CO_2 content reached what was practically its maximum, comparatively early in the reaction to ammonium chloride. Continued administration of the acid producing substance had but little further effect on the CO_2 content of the blood. This is probably due to the fact that the other regulating mechanisms came into play, and thus protected the CO_2 contents, and most certainly the pH, from further reduction. Accord-

CHART VII. Case E.C. Changes in calcium and phosphorus content of serum.

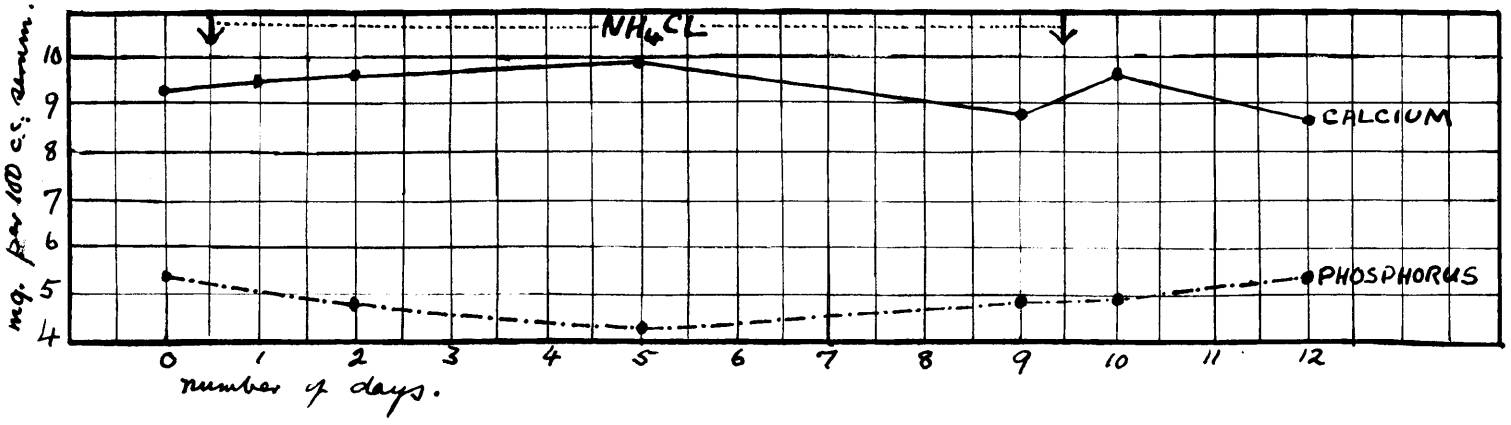
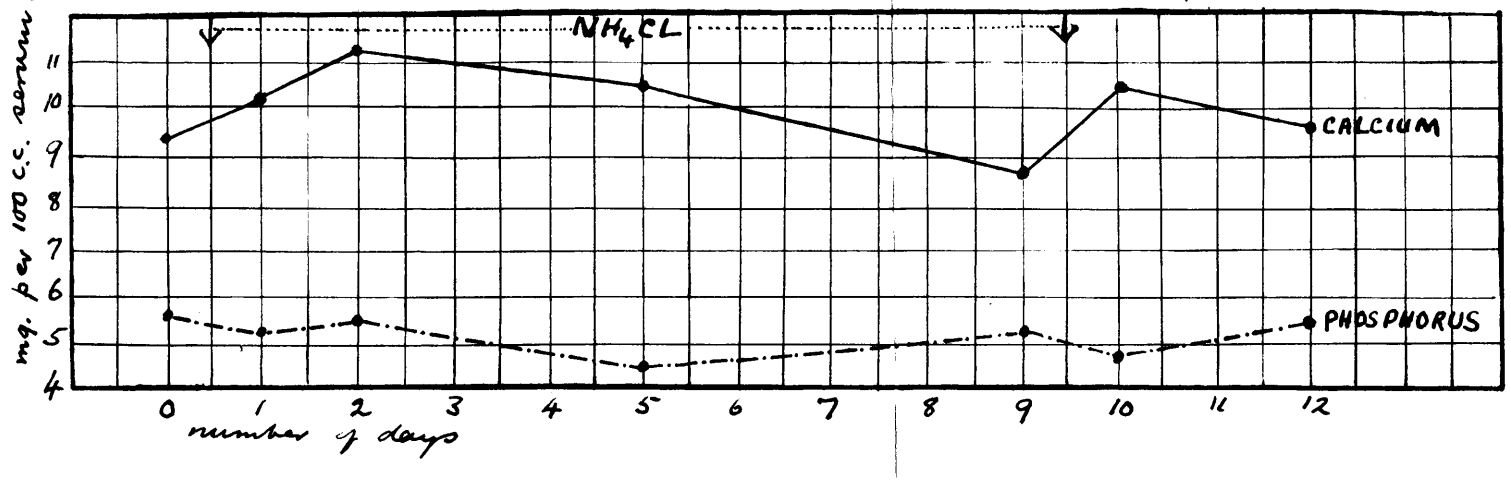


CHART VIII. CASE A.M. Changes in calcium and phosphorus content of serum.



ingly, if in any case the CO_2 content of the blood persistently falls from day to day, it would indicate that the other regulating reactions are unable to cope with the amount of acid produced.

B. Calcium and Phosphorus. (Table XI, columns 2 and 3).

In 1924 Stewart and Haldane (44) noted a 10 per cent rise in the serum calcium of a healthy adult, following the administration of 25 grm ammonium chloride. Haldane, Wigglesworth and Woodrow (45) found no significant change in the inorganic phosphorus content of the serum during acidosis but observed a slight fall as the acidosis was passing off. In the results recorded in Table XI where the estimations were made after a variable period from the commencement of the acidosis, no constant change in either calcium or phosphorus was observed. In the other 2 subjects (Charts VII and VIII) more frequent analyses were made. In both the serum calcium showed an initial rise which persisted till the 5th day, thereafter falling below the normal level: on the cessation of ammonium chloride administration the calcium immediately rose somewhat above the control level and then returned to normal. The serum phosphorus moved in the inverse direction to calcium.

TABLE XII.

Showing intake, output and retention of chlorine (c.c. N /10.).

Name.	Period	Intake	Output		Retention.	
			Urine	Faeces	Total	Per kg. per day.
N.G.	Normal	4133	3585	36	+512	+2.8
	NH_4Cl.	10675	9518	40	+1117	+6.1
W.C.	Normal	4133	3815	15	+303	+1.6
	NH_4Cl.	10675	9853	17	+805	+4.3
J.F.	Normal	2755	2829	–	-74	-0.6
	NH_4Cl.	8365	7299	–	+1066	+8.8
	NH_4Cl.	8365	7656	–	+709	+5.8
N.M.	Normal	4018	3706	–	+312	+1.5
	NH_4Cl.	10560	10040	–	+635	+3.0
	NH_4Cl. (5 days)	7545	7678	–	-133	-0.9

TABLE XIII.

Percentage excretion of chlorine in first 24 hours following ingestion of sodium chloride.

Amt. of NaCl. given in gm.	Form in which NaCl. given.	Diet	% excretion of extra salt during 1st. 24 hours.
4.5	Saline	Salt poor	53
4.5	Saline	Salt rich	62
10.0	Solid in capsule	Salt poor	50
10.0	Solid in capsule	Salt rich	67

Urinary Excretion of Chlorine: The excretion of chloride normally takes place through the urine and the sweat. The faecal output is practically negligible. It was estimated in two of our cases, and as will be seen from the results in Table XII the faecal excretion of chloride was relatively minute both during the control and ammonium chloride periods.

During the control period there was a small retention of chlorine except in the case of J.F. where there was a very slight negative balance. While ammonium chloride was being administered the retention was increased in every case except during the second period of N.M. which was characterised by a slight negative balance.

When one comes to examine the daily figures it is plain that all the subjects reacted immediately to the extra chlorine by the excretion of a greatly increased amount of this substance in the urine. In N.G. the output was doubled on the first day, so that only about 30% of the extra chlorine had been retained. This corresponds to what happens when sodium chloride is given. Table XIII indicates the percentage excretion of chlorine in the first twenty four hours following ingestion of sodium chloride: the subject was a healthy boy aged 11 years.

CHART IX. Case N.S. Daily urinary output of water, chlorine, fixed base, ammonia and titratable acid.

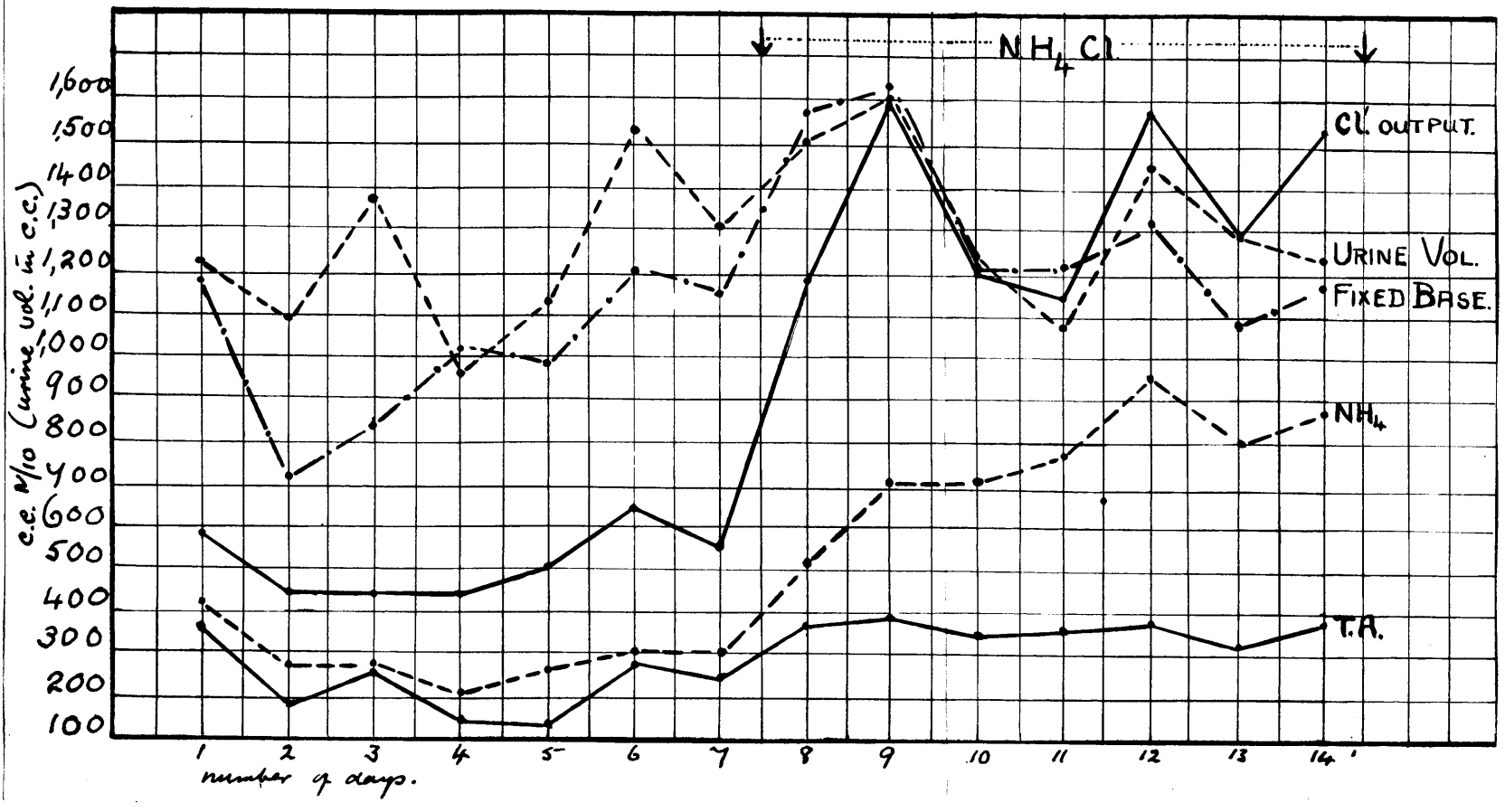


CHART X. Case W.C. Graph showing daily out-put of water, chlorine, fixed base, ammonia and titratable acid.

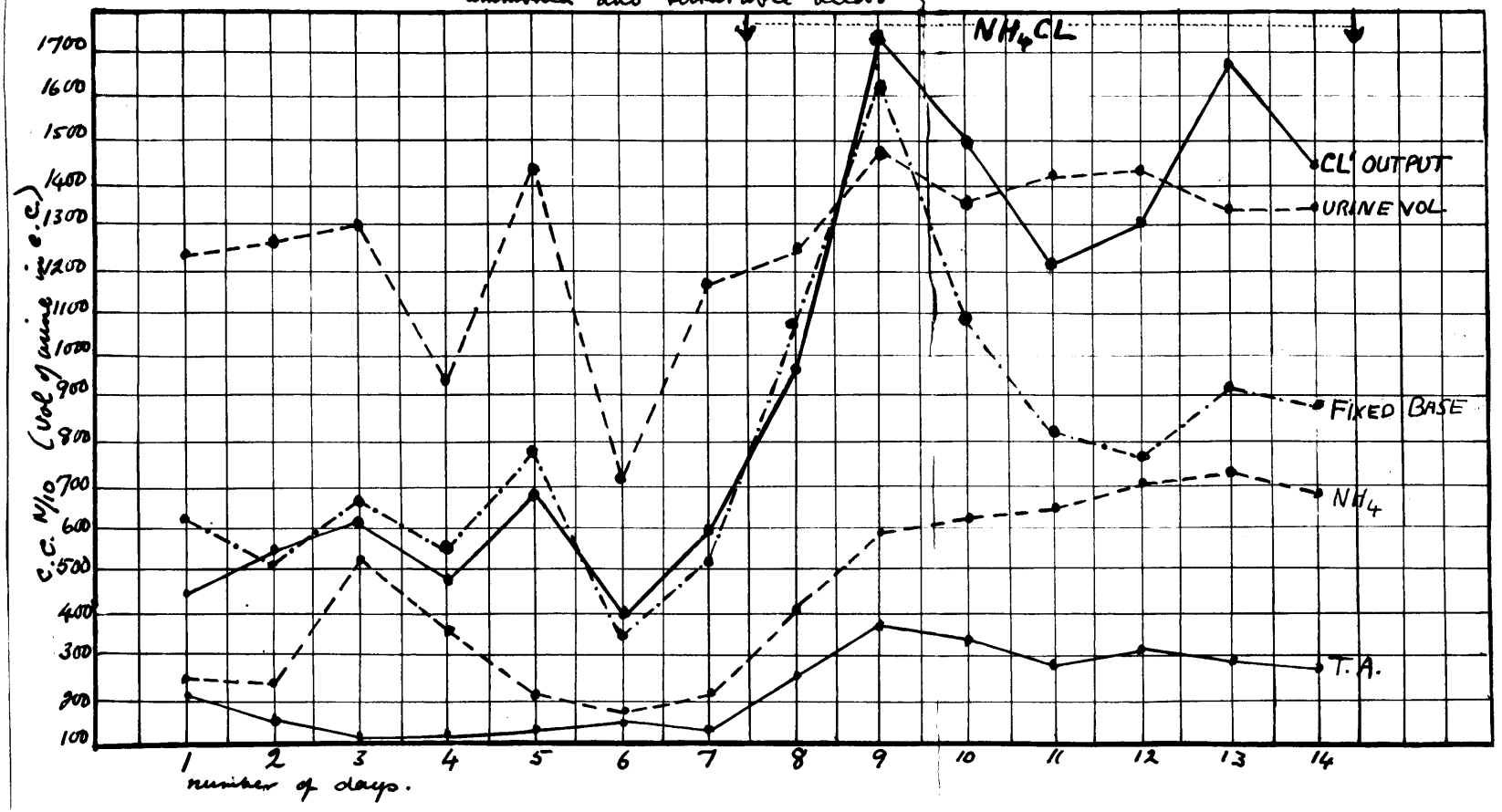


CHART XT. Case J.F. Graph showing daily urinary output of water, chlorine, fixed base, ammonia & titratable acid.

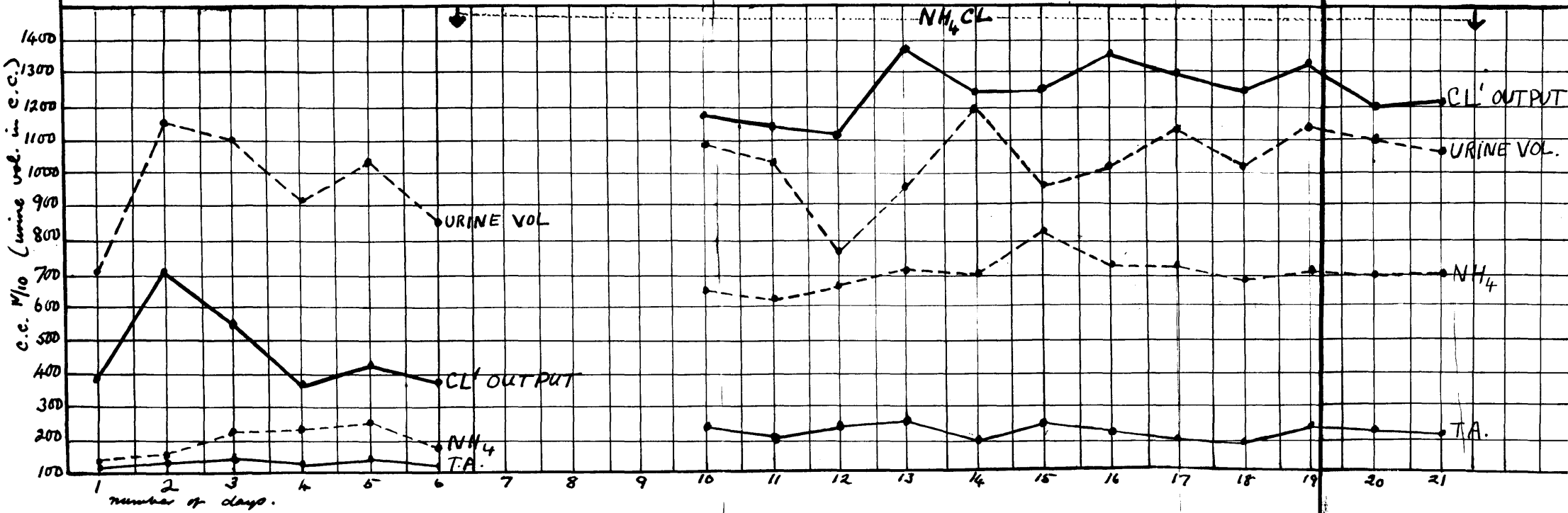
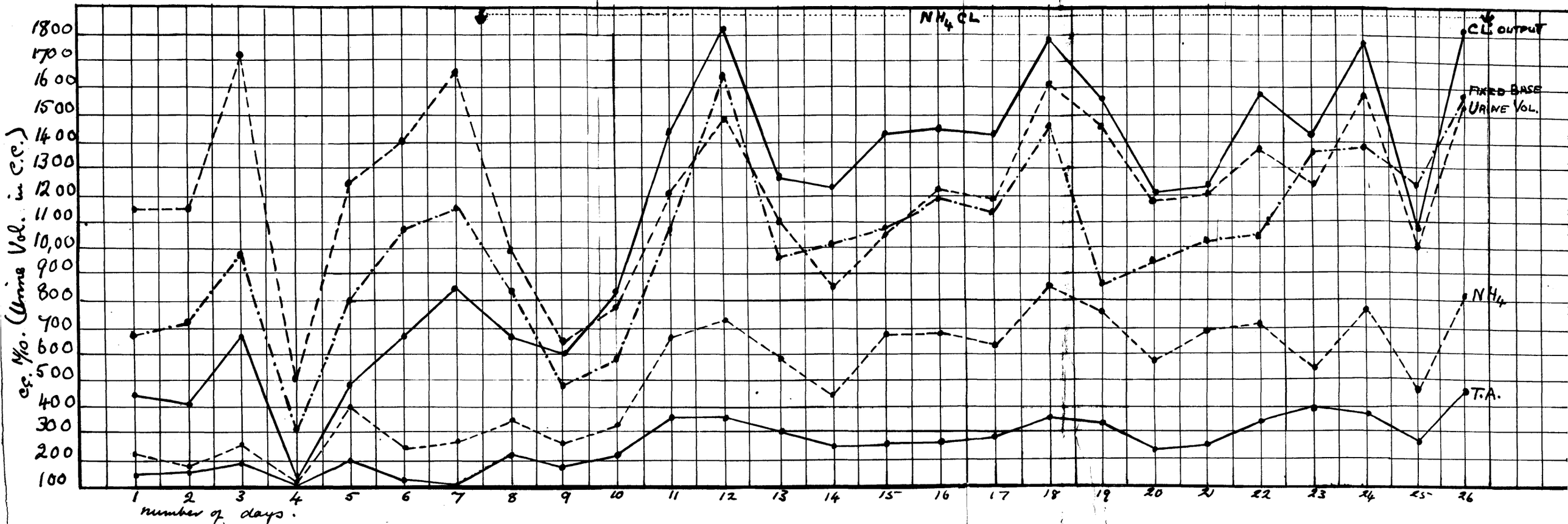


CHART XII CASE N.M. showing daily output of water, chlorine, fixed base, ammonia and titratable acid.



With the exception of N.M. the daily curve of NaCl output (Charts IX to XII) during administration of ammonium chloride shows that the peak of chloride excretion occurred on the second or third day. This was followed by a drop lasting over 2 or 3 days, which was succeeded on the fifth or sixth day by a peak reaching almost to the level of the first. In the case of N.M. there was a complete absence of the first peak but the second was quite marked. It will be noted in every case that this second peak corresponded with the maximum rise in the output of ammonia. It is therefore fair to conclude that this secondary rise in the excretion of chlorine was due to the increased ability of the kidney to supply ammonia. Indeed, a glance at the chlorine and ammonia curves following this second peak shows in every case a fairly marked parallelism indicating a correlation between these two substances. This parallelism is not noticeable during the first 5 days of ammonium chloride administration. There is also a fairly marked correlation between the amount of urinary chloride and fixed base both during the control and the ammonium chloride periods, with the exception of the control period of N.G. The urinary volume and chlorides also show some parallelism especially during the

ammonium chloride periods.

Urinary Volume: Gamble, Ross and Tisdall[46] reported an increase of urinary volume in children during the administration of either calcium or ammonium chloride. Keith and Whelan[43], however, found no change in the volume of urine excreted by a normal individual during ingestion of ammonium chloride. During such administration there was in all our cases except the first period of N.M. an increase in urinary volume, not, however, as marked as might have been expected. The daily output of urine varied greatly, frequently falling much below the maximum observed in the control period.

Ammonia and titratable acidity of the urine:

The output of ammonia and titratable acid was increased in every case during the administration of ammonium chloride. The maximum output of titratable acid was reached by the second day, following which there was usually a very gradual decline in the output. The ammonia content of the urine did not attain its greatest value till the fifth or sixth day, and in the case of J.F. the ninth day. Thereafter the output of ammonia remained at a constant level, except in the case of N.M. where considerable variations were observed from day to day. The ammonia output was not estimated in the days following the ammonium chloride period, but Gamble[46] and others have

TABLE XlV: Showing Intake, faecal and Urinary Outputs, and retention of Calcium and Phosphorus (Grm.)

NAME.	PERIOD		TOTAL INTAKE		FAECAL OUTPUT		URINARY OUTPUT		% OF TOTAL OUTPUT IN URINE.		TOTAL Retention		RETENTION per kgrm. per day.	
	INTAKE	DAYS	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5
N.G	Normal	7	20.16	27.72	9.508	6.818	1.406	11.55	12.8	62.8	9.246	9.352	.05	.05
	NH_4Cl.	7	20.16	27.72	12.445	8.984	2.949	12.222	19.0	57.6	4.766	6.514	.025	.034
W.C.	Normal	7	20.16	27.72	14.983	14.390	1.521	9.464	9.2	39.7	3.66	3.87	.018	.019
	NH_4Cl.	7	20.16	27.72	15.938	14.564	2.60	12.600	14.0	46.4	1.62	0.56	.008	.002
J.F.	Normal	6	13.44	18.48	8.621	7.494	0.683	7.686	7.3	50.6	4.136	3.30	.034	.027
	NH_4Cl.	6	13.44	18.48	11.158	9.564	2.133	7.812	16.0	44.9	0.149	1.104	.001	.009
	NH_4Cl.	6	13.44	18.48	8.823	7.728	2.099	7.392	19.0	48.9	2.518	3.36	.021	.028
N.M.	Normal	7	19.60	26.95	10.959	9.627	1.784	11.102	14.0	53.5	6.857	6.121	.033	.029
	NH_4Cl.	7	19.60	26.95	19.649	17.445	3.192	11.928	13.7	40.7	-3.241	-2.759	-.015	-.013
	NH_4Cl and cod-liver oil.	5	14.00	19.25	17.799	16.425	2.829	10.212	13.7	38.3	-6.608	-7.387	-.044	-.050

TABLE XV: showing ash, calcium, phosphorus and fat content of Faeces.

NAME.		PERIOD 1 (Normal) Total quantity in faeces grm.	% in faeces	Period 2 (NH_4Cl.) Total quantity in faeces grm.	% in faeces
N.G.	Faecal Weight	62.55		66.55	
	Ash		31.8		36.2
	CaO	9.508	15.0	12.445	18.0
Weekly	P_2O_5	6.818	10.9	8.984	13.0
figures	Total Fat	21.736	34.75	19.486	29.2
	Combined fatty acids	17.795	28.45	15.659	23.5
	Free Fatty Acids	1.189	1.9	1.637	2.4
	Neutral fat	2.752	4.4	2.189	3.2
W.C.	Faecal Weight	84.65		88.40.	
	Ash		40.8		41.0
	CaO	14.983	15.0	15.938	18.0
Weekly	P_2O_5	14.390	14.0	14.564	14.0
figures	Total Fat	29.527	33.7	24.699	27.9
	Combined fatty acids	17.437	20.6	14.003	15.8
	Free fatty acids.	6.833	8.19	7.284	8.2
	Neutral Fat	4.156	4.91	3.412	3.8

NAME.		PERIOD 1(Normal) Total quantity in faeces grms	% in faeces	2(NH_4Cl) Total quantity in faeces grms.	% in faeces	3 (NH_4Cl) Total quantity in faeces grms.	% in faeces
J.F.	Faecal Weight	56.35		79.70		60.85	
	Ash		33.2		31.5		32.8
	CaO	8.621	15.3	11.158	14.0	8.823	14.5
6-day	P_2O_5	7.494	13.3	9.564	12.0	7.728	12.7
figures	Total Fat	20.70	36.79	33.386	41.89	20.00	32.9
	Combined fatty acids	14.01	24.95	18.18	22.81	12.64	20.8
	Free fatty acids	4.89	8.652	13.047	16.37	5.57	9.1
	Neutral Fat	1.80	3.188	2.16	2.71	1.78	2.9
N.M.	Faecal Weight	8.65		13.69		18.05	
	Ash		40.8		44.7		43.4
	CaO	1.565	18.0	2.807	20.0	3.556	19.0
daily	P_2O_5	1.375	16.0	2.492	18.0	3.285	18.0
figures	Total Fat	2.85	33.03	3.936	28.75	6.58	36.4
	Combined fatty acids	2.204	25.48	2.909	21.25	5.008	27.7
	Free Fatty acids	0.236	3.43	0.602	4.40	0.826	4.58
	Neutral Fat	0.376	4.12	0.424	3.10	0.743	4.12

shown that the output remains indefinitely above normal for some days following the administration of an acid salt.

Metabolism of Calcium and Phosphorus:

The intake and output of calcium and phosphorus in each case is detailed in Table XIV which also shows the retention and the partition of these substances between urine and faeces. In Table XV are given the results of the faecal analyses for calcium, phosphorus and fat.

It will be convenient to give a brief account of the results in each case, and thereafter to summarise and discuss the bearing of these findings on the general problem of mineral metabolism.

N.G. The retentions of CaO and P_2O_5 were reduced. The output of lime in the faeces was increased as the result of an increased percentage of CaO in the faeces and also a rise in the weight of the dried faeces. The urinary excretion of lime was also increased. The output of P_2O_5 by the urine was likewise raised, but the decreased retention of P_2O_5 was mainly the result of an increased faecal content of this substance. As with lime the rise in faecal phosphorus was consequent on an increased percentage output together with a rise in the faecal weight. The percentage of ash was also

increased, while the percentage and absolute amounts of total fat and combined fatty acids were decreased.

W.C. The results here were practically identical with those recorded above. One point of difference may be noted, namely, the fact that there was but little increase in the faecal output of P_2O_5, the lowering of the retention value being due to a fairly marked rise in the urinary content.

J.F. In this case there were 2 successive periods on NH_4Cl. The retentions of CaO and P_2O_5 were reduced during the first of the two periods but returned practically to normal in the second. There was a rise in the urinary CaO in both periods, and the urinary P_2O_5 in each was practically unchanged. The reduced retentions of lime and phosphorus were due entirely to the increased faecal output resulting from a rise in the faecal weight; the percentage of ash, calcium, and phosphorus were all reduced. The percentage of total fat in the faeces was increased during the first period because of the marked increase in free fatty acids while in the second period the value for total fat was slightly below that of the normal. The percentage of combined fatty acid was reduced during both periods.

N.M: With this subject there were two periods on NH_4Cl, the first for 7 days and the second for 5 days during which time 1 dram of cod-liver oil was given 3 times daily in addition. A negative balance of both lime and phosphorus was found during each NH_4Cl period, being much more marked on the second. The urinary output of lime and phosphorus was increased on both occasions, the increase in urinary phosphorus being much more marked in the second of the 2 periods. The percentages of lime, phosphorus and ash in the faeces were increased, but the marked rise in the total faecal output of CaO and P_2O_5 was chiefly the result of the striking increase in the weight of dried faeces. In the first period the percentages of total fat and combined fatty acids were reduced but in the second, during which cod-liver oil was also administered, these percentages were increased slightly above those found in the normal period.

Summary. There was in all cases a reduced retention of lime and phosphorus resulting from an increased output of these substances in both urine and faeces.

(a) Calcium. Goto (47) found in acidosis an increased excretion of calcium by the urine but Keith and Whelan observed but little change in the urinary excretion of

calcium during administration of ammonium chloride. In our cases, however, the urinary calcium was at least doubled and in one instance trebled. The increased faecal excretion of calcium was due to an increase in the total faecal weight and, with the exception of J.F., an increase in the percentage of lime in the faeces. Generally the increase in faecal calcium was much greater than that obtained in the urine. In W.C., however, the urinary and faecal increases were approximately equal, and in J.F. (2nd period) the urinary increase exceeded that in the faeces.

(b) Phosphorus. The extra output of phosphorus was even less consistently distributed between urine and faeces than was the extra lime. In only one case (W.C.) was the increase in urinary phosphorus marked. Apart from this case, in which the rise in faecal phosphorus was insignificant the main increase in excretion was by the faeces.

(c) Weight of dried faeces. In all cases there occurred an increase.

(d) Ash. With the exception of J.F. (1st period) there was always a rise in the percentage of ash in the dried faeces.

(e) Faecal fat. The percentage of total fat in the faeces was reduced in all cases except J.F. (1st period)

and N.M. (2nd period). The percentage of combined fatty acids was reduced in all cases except N.M. (2nd period).

Discussion. In spite of the large amount of work done in connection with calcium metabolism there is as yet no definite information as to the extent of absorption of this element, and it is still a matter for conjecture how much of the faecal calcium has been absorbed and excreted through the bowel wall, and how much has passed through the gut unabsorbed. Grosser (48) found that subcutaneous injection of calcium salts lead to an increased excretion by the bowel, and Salvesen (49) showed that in parathyroidectomised dogs nine-tenths of the calcium chloride injected intravenously was excreted in the faeces and one-tenth in the urine. Percival and Stewart (50) isolated the large intestine in cats and found that the intravenous administration of calcium chloride was followed by a marked increase in the excretion of calcium by the large intestine, but no change in the urinary output. Recently Bauer, Allbright and Aub (51) have published the results of an investigation of the calcium metabolism on a very low calcium intake in 13 normal adults. On these 13 subjects there were 46 three-day periods of investigation. With the exception

of a single period in one case, they found in all a negative balance of calcium, and with the exception of 3 periods there occurred in the faeces a greater amount of lime than had been ingested. In one case (N.M.) of our series during each of two periods on ammonium chloride there was a greater amount of calcium in the faeces than had been ingested. From these results it is justifiable to conclude that in ammonium chloride acidosis excretion of calcium through the bowel wall can occur. Our results also contradict the statement of Givens and Mendel (52) that the increase in urinary calcium in acidosis is the result of diversion of lime from stools to urine. In our cases both the urinary and faecal lime was increased in amount.

In one period at least (N.M., 3rd period) there was unequivocal evidence of calcium excretion by the bowel wall.

The investigations of Nelson (53) on the mineral metabolism of patients suffering from diabetes and of epileptic subjects fed on ketogenic diets have shown that the kidneys are capable of excreting large amounts of lime. Indeed, more than half the total excretion of calcium may take place through the urinary system.

In these cases there is also a slight increase in the faecal output of lime. The presence of an acidosis, therefore, leads to an increased excretion of lime both by urine and faeces. In our series, with the exception of N.M., the percentage of lime excreted by the urine is always increased during the ammonium chloride period. This would suggest that the amount of calcium excreted by the kidneys is to some extent dependent on the degree of acidosis. Additional support would at first glance seem to be lent to this view by the results of Shohl and Sato,[54] and Bogert and Kirkpatrick.[40] The former found that the addition of sodium bicarbonate to the diet decreased the urinary output of CaO and P_2O_5, but increased their content in the faeces to such an extent that the retention of each was reduced. Bogert and Kirkpatrick[40] record similar results with a base-forming diet. The addition of sodium bicarbonate to the diet brings in another factor, already referred to in a previous section, namely, a change in the reaction of the lumen of the gut. The decreased urinary output of calcium during administration of bicarbonate may be entirely due to the local effect of this salt in interfering with the absorption of lime by increasing the pH of the intestinal contents.

Attention has already been drawn to the theory advanced by Freudenberg and György[3] [5] that the decreased retention of calcium in rickets is due to an acidosis of the tissues which interferes with the precipitation of calcium salts. If this view were correct one would expect the mode of excretion of lime and phosphorus to be similar to that found during ammonium chloride acidosis. Quite the reverse obtains, since the output of lime in the urine is markedly diminished, as is also the urinary phosphorus; and the very low retention of these minerals is caused entirely by the large faecal content of CaO and P_2O_5. In other words, the partition of calcium and phosphorus in the excreta in rickets closely resembles that found in conditions tending to alkalosis rather than acidosis.

Part 2. Animal Experiments on the Intestinal Excretion of Calcium.

It has been shown in Part I that under the influence of acidosis induced by ammonium chloride calcium is, in at least small amounts, excreted by the bowel. The following experiments were carried out in an attempt to answer the question of how much of the faecal calcium under normal conditions is excreted by the gut and how much is the unabsorbed residue of the intake.

The animals chosen for the experiments were pigs and the method of procedure was to isolate a portion of intestine and analyse the contents for lime making at the same time a complete analysis of the intake in the food and the output in faeces and urine of CaO and P_2O_5. After recovery from the operation and before the metabolic studies were begun the isolated loop of bowel was washed out daily for a week and the washings discarded. During the metabolic studies the loop was washed out daily with a fixed quantity of distilled water, the washings dried and analysed for CaO. It was considered that this would give a fairly accurate quantitative determination of the lime excreted by the isolated portion of gut. Unfortunately it was found impossible to prevent loss of secretions from the ends of the loop during the intervals from washing.

Pig I. The first metabolic study was made when the animal was 9 weeks old. The diet consisted of 400 c.c. cow's milk, 400 gm. oatmeal, 8 gm. $CaCO_3$, 5 gm. NaCl and distilled water ad lib. During the 7-day period of study the weight increased from 12.3 to 13.0 kilos. At the age of 12 weeks the operation was carried out under chloroform anaesthesia. About 30 cm. of large intestine immediately distal to the caecum was isolated, one end closed and the other brought to the surface of the abdomen. The continuity of the remainder of the large intestine was restored by means of a lateral anastomosis. The animal made a rapid recovery. When $14\frac{1}{2}$ weeks old the second metabolic study was begun. One week before this 7-day period the diet was increased to 600 c.c. cow's milk, 600 gm. oatmeal, 10 gm. $CaCO_3$, 5 gm. NaCl and distilled water ad lib. The weight during this study increased from 13.8 to 15.3 kilos. At the end of this period 5 grams ammonium chloride daily were added to the diet and 3 days later the third 7-day period was begun. The weight during this period increased from 15.4 to 16.2 kilos. That the animal now suffered from a marked acidosis is shown from the analyses of the blood CO_2 which fell from 47.1 vols.% before the administration of ammonium chloride

TABLE XVl. Pig. 1. Intake, output and retention of CaO and P_2O_5.

		1st. Period Normal	2nd. Period Normal	3rd. Period. NH_4Cl.
Total Intake (in gm.)	(CaO	38.108	49.322	49.322
	(P_2O_5	34.16	51.240	51.240
Faecal Weight (gm.)		241.15	370.7	371.50
Percentage Ash		17.9	18.9	19.8
Output in faeces (gm)	(CaO	17.122	26.505	28.605
	(P_2O_5	13.625	23.354	25.26
Excretion of CaO into isolated loop (gm)		--	.030	.037
Output in Urine (gm)	(CaO	1.926	1.434	1.556
	(P_2O_5	1.541	2.347	2.956
Retention (gm)	(CaO	19.060	21.383	19.161
	(P_2O_5	18.994	25.539	23.024
Daily Retention per kilo (gm)	(CaO	.215	.210	.173
	(P_2O_5	.214	.251	.208

TABLE XVll. Pig.III. Intake, output and retention of CaO and P_2O_5

		1st. Period Normal	2nd. Period. NH_4Cl.
Total Intake (gm)	(CaO	50.33	11.13
	(P_2O_5	49.56	49.56
Faecal Weight (gm)		359.0	368.06
Percentage ash		14.8	10.8
Output in faeces (gm)	(CaO	18.147	6.257
	(P_2O_5	17.770	13.066
Excretion of CaO into isolated loop (gm.)		.0085	.014
Output in Urine (gm)	(CaO	2.603	1.345
	(P_2O_5	1.330	14.480
Retention (gm)	(CaO	29.580	3.529
	(P_2O_5	30.46	22.0136
Daily Retention per kilo (gm.)	(CaO	.241	.023
	(P_2O_5	.249	.146.

to 28.8 vols.% towards the end of the period. A radiogram taken of the bones showed no evidence of rickets.

Pig II. In this animal no metabolic study was made before the operation which was carried out when the pig was 10 weeks old. Under chloroform anaesthesia 60 cm. of small intestine 6" above the ileo caecal junction were isolated and the 2 ends brought to the surface of the abdomen. The continuity of the rest of the gut was restored by a lateral anastomosis. This animal also made a quick recovery. During the first metabolic study the diet given was the same as that given to Pig I during the second period. The weight increased from 17 kilos to 17.9 kilos. Five grams of ammonium chloride daily were then added to the diet, the calcium carbonate omitted, and 3 days later the second period was begun. The blood CO_2 fell from 51.2 vols.% to 31.4 vol.% during this study and the weight increased from 21 to 22 kilos.

Results. The results of the experiments on Pig I are given in Table XVI and on Pig II in Table XVII. In Pig I where a loop of large intestine had been isolated and the intake of lime kept constant,

(1) there is a very small amount of lime excreted by the large intestine.

(2) The amount excreted is increased 23% during ammonium chloride administration, but this amount constitutes only .78% of the total lime found in the faeces.

(3) It would seem that the total increase in faecal lime during ammonium chloride administration (2.1 gm.) cannot be accounted for by re-excretion into the large intestine, an increase of only .007 gm. CaO being obtained from the 30 cm. of isolated gut which represents a calculated equivalent of .18 gm. for the whole of the large intestine (the total length of the large intestine being equal to 760 cm). As has already been remarked, however, there was an unavoidable loss of secretions from the open end of the loop so that the actual excretion of calcium was probably higher than this figure would indicate.

In Pig II where a loop of small intestine had been isolated and the intake of CaO reduced during the second period to one-fifth of that during the first period,

(1) There is a definite though small amount of lime present in the secretions of the small intestine.

(2) There is a slightly increased amount of lime found in the intestinal secretions during administration of ammonium chloride in spite of the greatly reduced intake of lime.

Other 3 points of interest arise from a consideration of the figures obtained in the case of this animal. Firstly,

there is a decrease in the percentage retention of lime from 58.8% of the intake during the first period to 31.7% of the intake during the second period when the calcium intake is low - a difference of 27.1%. This decrease must be attributed to the marked reduction in the intake of lime during this period as in the other animal where the intake of lime was constant there occurred during the administration of NH_4Cl only a slight decrease in the retention (from 43.3% of the intake to 38.8%). From this it would appear that there requires to be present in the gut of the young animal a large quantity of lime in order to ensure absorption of the relatively small amount necessary for the body requirements. Secondly, during the low calcium period while the total retention of lime is reduced to one-nineth of the retention during the normal period, the urinary excretion of CaO is reduced by one half. Lastly, there is a marked change in the mode of excretion of P_2O_5 on the low calcium diet. During the normal period 6.9% of the total P_2O_5 excreted is found in the urine while during the low calcium period 52.6% is excreted by the kidneys. That this increase in the urinary excretion of P_2O_5 is not due to the acidosis produced by ammonium chloride is shown from a study of the other animal where little change was produced in the mode of excretion

of P_2O_5 by the administration of ammonium chloride. This is further evidence that normally calcium binds phosphorus to the gut and thus limits its absorption.

It would seem probable from these experiments that the bulk of the calcium and phosphorus in the faeces is the unabsorbed residue of the intake, and further, that the amount of lime and phosphoric acid found in the urine is to a certain extent influenced by the degree of absorption of these substances from the intestine.

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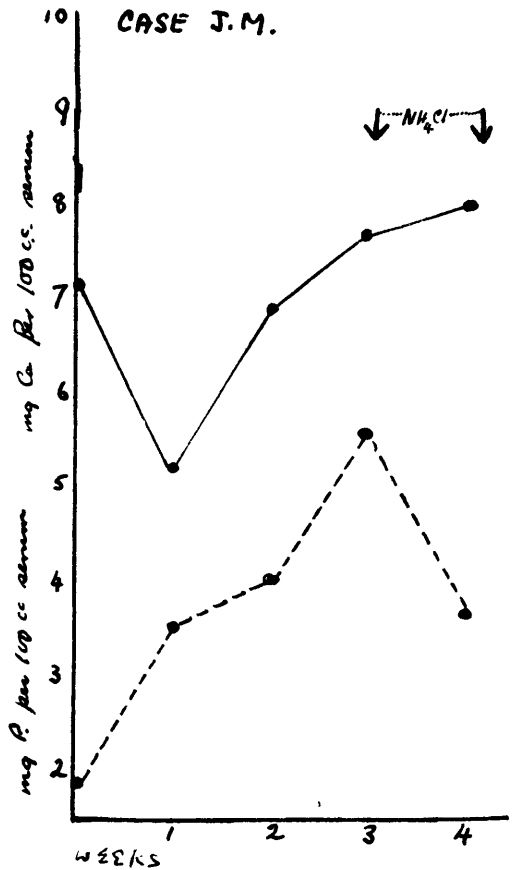
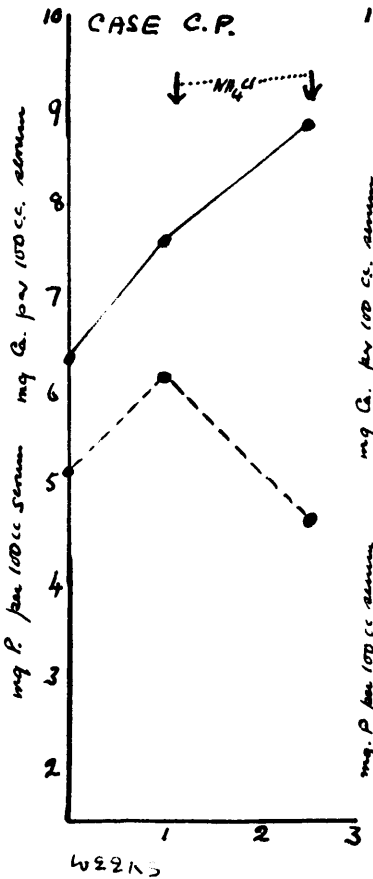
SECTION IV. The Metabolic Reactions of Rachitic Children to Acidosis produced by ammonium Chloride.

The subjects of this study were 4 children in 3 of whom the radiological picture showed a condition of active rickets. These 3 children also had signs of tetany, Chvostek's sign being positive in all 3 while one (C.P.) also had laryngismus. In the fourth child (M.R.) spontaneous healing was occurring at the time of the study. The metabolic investigations were carried out in a similar way to those made in the normal children and the same dose of ammonium chloride was given.

Clinical features: Like the normal children the cases of rickets showed no clinical signs of acidosis in spite of the large dosage and prolonged administration. R.M. was kept on ammonium chloride for $5\frac{1}{2}$ weeks without any apparent ill-effects. The radiological picture at the end of that time showed an appearance of early healing in spite of the fact that environmental and dietetic conditions were maintained constant. In all the active cases the signs of tetany disappeared during administration of the acid. In C.P. both laryngismus and Chvostek's sign disappeared after 3 days on NH_4Cl but returned the day after cessation of administration.

CHART XIII Changes in calcium and phosphorus content of the blood.





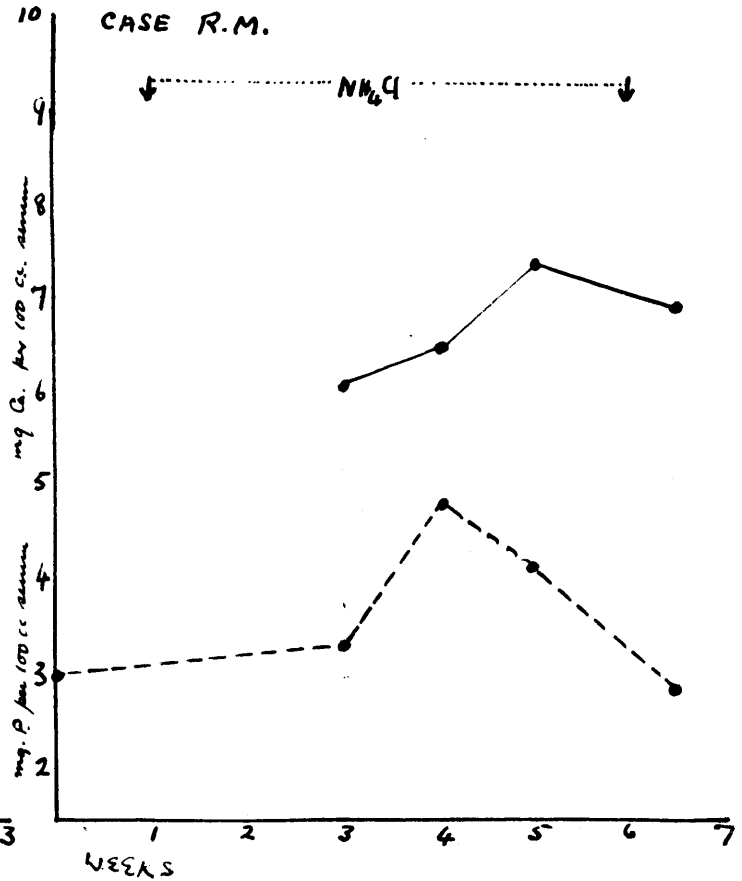


TABLE XVlll: Showing output of water, titratable acid, ammonia and chloride during Normal period and period on NH_4Cl.

Case	Period.	Volume c.c.	T.A. cc. N/10	NH_4 c.c. N/10	NaCl. gm.
R.M. Rickets (active & tetany)	1st. Per: (Normal) 6 days	1800	211.6	1224.4	5.780
	2nd. Period (NH_4Cl). 6 days	1860	450.0	1723.2	12.028
J.M. (active) RICKETS.	1st. (Normal) 7 days.	5485	711.6	2362.0	12.5341
	2nd. 7 days (NH_4Cl).	5510	1424.0	5496.2	39.0078
C.P. RICKETS (active & tetany)	1st. (Normal) 7 days.	4290	404.8	1042.8	10.6307
	2nd. (NH_4Cl.) 7 days	2355	162.0	3591.0	18.8400
M.R. (healing) RICKETS.	1st. (Normal) 7 days	4030 ~~4430~~	787.6 ~~956.2~~	1584.8 ~~2086.~~	11.5673 ~~11.7542~~
	2nd (NH_4Cl.) 7 days	4840 ~~4030~~	1516.0 787.6	5515. 1584.8	41.7650, ~~11.5673~~

TABLE XIX.

Showing the percentage of the extra chloride ingested which was excreted in the urine of normal and rachitic children during administration of NH_4Cl.

Rickets		Normal	
Case	% Extra Cl' excreted	Case	% Extra Cl' excreted.
R.M. Active rickets + Tetany.	19.4	N.G.	90.7
J.M. Active. RICKETS.	69.2	W.C.	92.3
C.P. Active rickets + Tetany.	21.4	N.M.	96.8
M.R. healing. RICKETS.	78.9	J.F.	80.0

Changes in Calcium and Inorganic Phosphorus Content of the Blood Serum. (Chart XIII).

In the 3 cases studied both the serum calcium and the inorganic phosphorus content of the serum tended to return to normal during the administration of ammonium chloride. The serum calcium which was abnormally low showed an increase which did not quite reach normal during the period studied, and the serum phosphorus which in two cases tended to be high at the beginning of the NH_4Cl period, fell during the period. In the third case the serum phosphorus initially low showed an increase for 3 weeks and then gradually fell. The change in the serum calcium in this series of cases is contrary to the results of Gamble and Ross who found that administration of ammonium chloride did not increase the lowered calcium content of the plasma found in tetany.

Urinary Excretion of Chlorine: The figures for the urinary excretion of chloride are given in Table XVIII. As in the normal children the urinary output of chloride increases during the ammonium chloride period. There is, however, a marked difference in the degree of increase. This becomes apparent from an examination of Table XIX where a comparison is made of the percentage of the extra Cl' excreted in the urine of the normal cases

TABLE XX.

Showing the excess of titratable acid and ammonia excreted in the urine during the NH_4Cl. period in normal and rachitic children.

Rickets			Normal		
Case	Excess T.A.	Excess NH_4	Case	excess T.A.	excess N
R.M. rickets active + Tetany	238.4	498.8	N.G.	917	3298
J.M. active Rickets.	712.4	3134.2	W.C.	1172	2452
C.P. rickets active + Tetany	242.8	2548.2	N.M.	1150	2768
M.R. healing rickets.	728.4	3930.4	J.F.	527	3051

TABLE XXl. Showing Intake, faecal and urinary outputs, and retention of calcium and phosphorus (gm.)

	PERIOD	INTAKE		FAECAL OUTPUT		URINARY OUTPUT		RETENTION		DAILY RETENTION PER. KILO.	
		CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5
Case 1. R.M. Active Rickets	1st. Per. [illegible]	8.208	10.80	6.915	5.301	.067	3.696	1.226	1.803	.030	.044
	2nd. Per. (On NH_4Cl)	8.208	10.80	6.293	4.644	.084	3.740	1.831	2.416	.045	.059
Case 2 J.M. Active Rickets	1st. Per. [illegible]	15.12	21.168	13.837	11.408	.116	7.772	1.167	2.996	.012	.021
	2nd. Per. (on NH_4Cl)	15.12	21.168	9.743	8.419	.205	8.436	5.172	5.321	.057	.047
Case 3 C.P. Active Rickets	1st. Per.	12.60	17.64	9.984	12.355	.092	2.32	2.524	3.805	.037	.044
	2nd. Per. (on NH_4Cl)	12.60	17.64	9.148	11.616	.146	2.754	3.306	4.110	.050	.057
Case 4 M.R. Healing Rickets	1st. Per.	12.60	16.38	7.076	4.946	.176	6.512	5.348	3.922	.075	.055
	2nd. Per. (on NH_4Cl)	13.02	16.80	9.284	7.346	.713	7.676	3.023	1.778	.041	.017

with the percentage of the extra Cl' excreted in the urine of the rachitic children. It will be seen that whereas the normal children excrete from 80% to 97% of the extra Cl' ingested, the children with active rickets excrete only from 19.4 to 69.2%, this figure rising to 78.9% in the healing case.

Urinary Volume: There was a slight increase in urinary volume in 2 of the cases during administration of ammonium Chloride but in C.P. the volume was greatly reduced being only about half that of the normal period. In the healing case the volume during the NH_4Cl period was reduced by about one-tenth, (Table XVIII).

Ammonia and Titratable Acidity of the Urine: In 2 of the cases of active rickets the acidity of the urine remained low during the administration of ammonium chloride, there being an actual decrease in the titratable acid during the NH_4Cl period in C.P. In the other active case and in the healing case the increase in T.A. was within the lower limit of normal. The figures for the increase in ammonia output are normal except in R.M. where the increase is only slight. (Tables XVIII and XX).

Metabolism of Calcium and Phosphorus: The intake and output of CaO and P_2O_5 is detailed in each case in Table XXI which also shows the retention and the partition of these substances between urine and faeces. In

TABLE XXII: Showing Ash, Calcium, phosphorus and fat content of faeces

NAME		PERIOD 1 (Normal) Total quantity in faeces gm.	% in faeces	PERIOD 2 (NH_4Cl.) Total quantity in Faeces gm.	% in faeces
R.M.	Faecal weight	46.1		43.40	
Active	Ash		31.4		29.7
Rickets	CaO	6.915	15.	6.293	14.5
Tetany	P_2O_5	5.301	11.5	4.644	10.7
Weekly	Total Fat	19.929	43.23	18.857	43.4
Figures	Combined fatty acids	15.314	33.22	12.551	28.9
	Free fatty acids	3.298	7.155	5.859	13.5
	Neutral Fat	1.316	2.855	0.447	1.0
J.M.	Faecal Weight	73.6		52.95	
Active	Ash		40.		40.
Rickets	CaO	13.837	18.8	9.743	18.4
Tetany	P_2O_5	11.408	15.5	8.419	15.9
Weekly	Total Fat	20.939	28.45	17.542	33.1
figures.	Combined Fatty acids	12.622	17.15	10.521	19.8
	Free fatty acids.	5.961	8.1	5.004	9.4
	Neutral Fat	2.355	3.2	2.017	3.8
C.P.	Faecal Weight	62.4		72.6	
Active	Ash		45.		45.
Rickets	CaO	9.984	16.0	9.148	12.6
Tetany	P_2O_5	12.355	19.8	11.616	16.0
Weekly	Total Fat	17.515	28.07	18.411	25.3
Figures.	Combined fatty acids	1.622	2.60	1.365	1.8
	Free fatty acids	12.299	19.71	10.781	14.8
	Neutral fat	3.594	5.76	6.265	8.6
M.R.	Faecal Weight	36.1		45.07	
Healing	Ash		38.2		42.1
Rickets	CaO	7. 076	19.6	9.284	20.6
Weekly	P_2O_5	4.946	13.7	7.346	16.3
figures.	Total fat	6.743	18.68	7.310	16.2
	Combined fatty acids	4.498	12.46	4.439	9.8
	free fatty acids	0.975	2.7	1.767	3.9
	neutral fat.	1.270	3.52	1.104	2.4

Table XXII are given the results for the faecal analyses for CaO, P_2O_5 and fat. In all cases there was an increased output of CaO and P_2O_5 in the urine - a slight increase in the case of active rickets and a very marked increase in the case of healing rickets particularly in the output of CaO which was increased roughly 4 times. The faecal output of CaO and P_2O_5 was reduced in the active cases and increased in the healing case. In R.M. the decrease was contributed to partly by a reduction in faecal weight and partly by a reduction in the percentage composition of CaO and P_2O_5 in the faeces. In J.M. the reduction in faecal weight was the chief factor and in C.P. the reduction in the percentage of CaO and P_2O_5 in the faeces seemed responsible. In the case of healing rickets the increased output of CaO and P_2O_5 was due to an increased faecal weight and an increase in the percentage of these substances in the faeces. The retention of both CaO and P_2O_5 was increased in all the active cases and diminished in the healing case. No constant change occurred in the fat content of the faeces. It is interesting to note that in both periods of C.P., who had the most marked signs of tetany, the P_2O_5 content of the faeces was excessively high and the combined

TABLE XXlll: A comparison of the Metabolic reactions of normal and rachitic children to acidosis produced by ammonium chloride.

		NORMAL	Active Rickets	Healing Rickets
URINE	Average increase in T.A.	941	236	788.4
	Average increase in NH_4	2892	2060.7	3930.4
	% of the excess Cl^- excreted	90	36.6	78.9
	Excretion of CaO	increased	increased	greatly increased
	Excretion of P_2O_5	increased	increased	increased
FAECES	Excretion of CaO	increased	decreased	increased
	Excretion of P_2O_5	do	do	do
RETENTION	CaO	decreased	increased	decreased.
	P_2O_5	do	do	do

fatty acids were very low.

A comparison of the reaction to ammonium chloride of this series of cases with the reaction of the normal series is made in Table XXIII. The following points are to be noted:-

1. Administration of ammonium chloride increases the retention of CaO and P_2O_5 in active rickets.
2. The increase in urinary excretion of titratable acid and ammonia is on the whole not so great in the rachitic children as in the normal.
3. Whereas the normal subject excretes in the urine almost all the extra Cl' ingested, the cases of rickets excrete only a small amount.
4. In the healing case the reaction to ammonium chloride as regards urinary output of titratable acid and ammonia, and retentions of CaO and P_2O_5 resembles the reaction found in the normal cases.

Discussion: It has already been pointed out that in rickets the metabolic picture as regards calcium and phosphorus resembles more the picture met with in alkalosis than that met with in acidosis. But from the experiments described in the second part of Section III we have evidence that a diminished intake, resulting most probably in a diminished absorption of lime, leads to a reduction in the kidney excretion of this substance. There is a certain amount of evidence that there is a disturbance in absorption of calcium and phosphorus from the gut in rickets due to an increased pH of the intestinal contents. The problem is how far this disturbance is responsible for the low urinary output of calcium and phosphorus in rickets and whether we can demonstrate any disturbance in intermediary metabolism which may play a part.

The first striking difference between the reaction of rachitic and normal cases to the administration of ammonium chloride is the increase in the retention of lime and phosphorus in the former, and the reduction in the latter. Although ammonium chloride was chosen as an acid-producing substance because of its neutrality in the gut, the generalised acidosis produced throughout the body would probably secondarily affect the reaction in the intestine. In this way absorption of the mineral

elements would be facilitated. This, however, does not explain why the rachitic tissues hold on to the extra lime and phosphorus absorbed, while normal tissues under the influence of acidosis actually lose some of their normal mineral content. The explanation may be simply that the important defect in rickets is interference with absorption. When the disturbance is rectified the mineral-starved bones can utilize some of the extra CaO and P_2O_5 absorbed, this increased utilization of the mineral elements by the rachitic bone masking the normal response to acidosis, namely an increased excretion of CaO and P_2O_5. An objection to this explanation is the reaction of the case of healing rickets to ammonium chloride. This reaction resembled that of the normal subject in that the retention of calcium and phosphorus was diminished. Healing was early in this case and there was still some osteoporosis as judged radiographically at the time of the study. The presumption is therefore that the acidosis causes some change which enables actively rachitic tissues to hold on to the calcium and phosphorus absorbed.

Before discussing the other findings it will be convenient to refer to the mechanism of the defence of

the body to acidosis. Against the production of a non-gaseous acidosis such as is produced by ammonium chloride the organism has the following general defences (1) an increase in the available base of the blood, (2) an increased excretion of volatile acid by the lungs and (3) an increased supply of base for neutralising acids that are to be excreted.

(1) Increase in available base of the blood. The fixed base is kept at a fairly constant level. By a decrease in the CO_2 content a certain amount of base is rendered free for neutralising other acid radicles. The amount of base released by these changes in such a condition as prevails in the present experiments is practically negligible.

(2) Increased excretion of volatile acid by the lungs.

Respiratory changes leading to an increased output of CO_2 must naturally follow the displacement of CO_2 from its union with base, otherwise the tension of CO_2 in the blood would increase and lead to the production of a CO_2 acidosis (gaseous).

(3) Supply of base for the excretion of acid. The kidney is undoubtedly the principal organ for the excretion of the non-volatile acid radicles. At the lowest possible value of the urinary pH chlorine cannot be excreted as

a free acid, but requires a full equivalence of base. This base can be obtained in 3 ways. (a) Base may be released from weak acids which can be excreted either free or with only a partial complement of base. (b) Extra ammonia may be formed. (c) Fixed base may be supplied from the tissues and tissue fluids.

(a) Release of base from weak acids. This is manifested by an increased acidity of the urine which decreases the base-combining powers of the weaker acids. Change of phosphate from the mono- to the di-hydrogen variety forms the best example of the saving of base effected in this way.

(b) Increase in ammonia formation. The work of Benedict and Nash (55) has shown that ammonia is formed in the kidney. In cases of marked renal inefficiency the ammonia output is low. In the subject with normal renal function the supply of ammonia forms a most important bulwark against acidosis. The increase in ammonia formation, however, takes some time to reach its maximum (see Charts IX to XII). Some mechanism is therefore required to tide over the needs of the excretory system for more base until the supply of ammonia is sufficient to meet the demands.

(c) Supply of fixed base from tissues and tissue fluids.

I along with Dr. Morris (56) have shown that until a sufficient supply of ammonia is formed the demand for

base is met by base derived from the bones and from the other tissues of the body. We have brought forward evidence to show that the increase in the output of calcium following the administration of ammonium chloride is the result of the response of the osseous tissues and forms a reaction of importance in the defence of the organism to acidosis.

Apart from the abnormal reaction of calcium and phosphorus already referred to, the reactions of the rachitic cases to ammonium chloride acidosis were abnormal in the following respects.

(1) There was a subnormal increase in the acidity of the urine.

(2) There was a subnormal increase in the excretion of chlorine.

(1) Subnormal increase in acidity of urine.

This might at first glance be considered as due to the diminished output of urinary phosphate in rickets, in this way less than the normal amount of phosphate being available for conversion from the mono- to the di-hydrogen salt. Actually this explanation does not hold as the increase which occurs in the urinary output of phosphate in the rachitic cases during acidosis is relatively high when compared with the low increase in

output of acid. Indeed in one of the cases the acidity of the urine is actually lower during the period of acidosis. It would appear therefore that in these cases there is a retention of acid.

(2) The Subnormal increase in excretion of chlorine.

Defective renal action is a possibility which must be considered in seeking an explanation for this finding. The increase in the output of ammonia by the kidney although subnormal in one case was within the lower limit of normal in the other two. In the absence of any other evidence of impairment of kidney function we must ascribe this retention of chlorine to a disturbance of intermediate metabolism. Because of the osteoporosis which is present in rickets the question arises as to what part a deficient supply of base in the form of calcium plays in the subnormal excretion of chlorine. In normal cases the extra amount of calcium excreted as base during ammonium chloride acidosis was calculated by Morris and ~~me (36)~~ in 2 cases as equivalent to 1/42 of the total extra base excreted during acidosis, as 1/19 and 1/16 in other 2, and as 1/9 in 1 case. As the excretion of the extra chlorine in the rachitic cases was roughly only 1/3 of the excretion in the normal cases it is obvious that a deficient supply of calcium as base cannot explain this enormously increased retention of chloride.

An interesting point to note is that accompanying the retention of chlorine there is not a corresponding retention of water as would be expected if chlorine were retained as an isotonic solution of NaCl. It may possibly be retained in an organic form. Protein metabolism in rickets has received but scant attention. Gassman (57) found the nitrogen content of rachitic bone normal and Meyer (58) reported that the addition of casein to the diet lowered the retention of calcium. These few experiments however throw no light on the subject and much work remains to be done in this field.

The clinical findings show that ammonium chloride did not in any way aggravate the condition of these rachitic children. Just as in the normal cases there were no clinical signs of acidosis. One must admit however that these cases were complicated by tetany and the beneficial effect of acid in cases of tetany is well known. Freudenberg (59) considers that infantile tetany is associated with a trend towards alkalosis caused by a slowing down of the metabolic rate and a consequent lack of formation of acid products, but Drucker (60) and others have found that the pH of the blood is normal in cases of infantile tetany. It would seem therefore that in tetany, as in rickets, there is no conclusive evidence

of any change in the acid-base equilibrium. The frequent association of these two diseases, however, suggests that any change which may be present is in the same direction in both conditions and not, as Freudenberg suggests, towards acidosis in rickets and towards alkalosis in tetany. If rickets were associated with a tendency towards acidosis it is difficult to understand why tetany should be such a frequent complication when this latter condition is so readily relieved by the administration of acid. In the present series of cases not only were the clinical signs of tetany abolished during administration of the acid, but in the one case who was given ammonium chloride for a prolonged period there was also radiographic evidence of improvement in the rachitic changes in the bones. The details of the X-ray photographs taken in this case are given below. The interpretation of these radiograms has been approved by Professor Leonard Findlay.

R.M. aet 2 years.

8.5.29 Admitted to hospital.

9.5.29 X-ray of Wrist: active rickets.

16.5.29 " " " I.S.Q.

23.5.29 " " " I.S.Q.

1.6.29 " " " I.S.Q.

6.6.29 " " " I.S.Q.

18.6.29 " " " I.S.Q.

19.6.29 Commencement of administration of NH_4Cl gmI 5 times daily.

29.6.29 X-ray of Wrist: I.S.Q.

30.6.29 Administration of NH_4Cl ceased.

10.7.29 X-ray of Wrist: definite signs of early healing.

24.7.29 " " " ? further advance in healing process.

31.7.29 Administration of NH_4Cl gm I 5 times daily again started.

12.8.29 X-ray of Wrist: definite advance in healing process.

22.8.29 " " " further healing.

29.8.29 " " " very slow healing progressing.

8.9.29 Administration of NH_4Cl ceased.

9.9.29 X-ray of Wrist: further healing.

All the evidence therefore, clinical, chemical and radiographic, which has been obtained in this investigation favours the view that in active rickets any change which may be present in the acid-base equilibrium of the tissues is towards the alkaline side and there has been found nothing to support the theory of increased acid production.

Conclusions.

1. There is a diminished excretion of lime and phosphorus by the kidneys in active rickets.
2. It would seem probable that there is a change in intestinal pH leading to an interference with absorption of calcium and phosphorus.
3. There is a disturbance in intermediate metabolism made manifest by the abnormal reaction to ammonium chloride of calcium, phosphorus, and chlorine.
4. There is a certain amount of evidence that acid may to some extent rectify this metabolic disturbance, namely (a) the increase in the retention of calcium and phosphorus following the administration of ammonium chloride, and (b) the appearance of slight healing in the one case in which administration of ammonium chloride was prolonged for several weeks.

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ADDENDUM.

Part I: The Estimation of the Phase of the Disease in Rickets.

In many diseases, particularly in those with a tendency to spontaneous cure, various therapeutic agents have been unjustifiably credited with possessing valuable curative properties. In no instance is this perhaps more striking than in the case of rickets, in which claims have been made for the efficacy of many different forms of treatment.

Much of the misunderstanding in the question in the case of rickets has arisen from the want of certainty in the examples tested whether the disease was in a progressive or a retrogressive stage. At the outset therefore of any investigation it is essential that we have standards by which this matter may be decided and this part of the work deals with that aspect of the problem, viz:- the relative value of different methods of determining the phase of the disease.

It has frequently been the custom to decide whether an individual example of rickets were active or healing from an isolated radiological examination. We have not infrequently noted, however, that a case of rickets which has been judged from a single radiological examination to be active may, within 2 to 3 weeks, and that in spite of

the conditions remaining the same, show unequivocal radiographic evidence of healing. Experience has taught us that it may also take this time after the inception of healing, or at least after the administration of efficient cod liver oil, before definite signs of healing are visible radiologically. It has been our custom, therefore, in order to establish the activity of the disease to require radiograms failing to reveal any evidence of healing taken at an interval of 3 weeks. But as this method involves the expenditure of a considerable amount of time, a pre-observation period of at least 3 weeks, it was hoped that a study of the behaviour of the inorganic phosphorus content of the blood serum and the retentions and modes of excretion of calcium and phosphorus might provide data on which to base a simple and time-saving but still reliable test of the stage of the disease.

Our findings from this point of view are considered under 2 headings, viz:- (a) that dealing with the inorganic phosphorus content of the serum, and (b) that dealing with the metabolism of calcium and phosphorus.

A. The Inorganic Phosphorus Content of the Blood Serum.

Many observations have been made on the variations of the inorganic phosphorus content of the blood serum in

rickets. Iverson and Lenstrup[61] in 1920 published the results of a study of the concentration of acid-soluble, acid-insoluble and total phosphorus of the plasma and whole blood of normal and rachitic infants. They found in the case of rickets that the acid soluble phosphorus was low. A year later Howland and Kramer[62] described a definite lowering of the inorganic phosphorus of the serum in active rickets. They based their diagnosis of the stage of the disease on clinical grounds supported by radiograms. In 16 non-rachitic children the inorganic phosphorus varied from 4 mg. to 7.1 mg. per 100 c.c. serum. In 22 rachitic children it varied from 0.6 to 3.2 mg. per 100 c.c. serum. From a study of the calcium and inorganic phosphorus of the serum in children with uncomplicated rickets and with rickets complicated by tetany Howland and Kramer were led to believe that the determining factor in the calcification of the bones is the presence of calcium and phosphorus in such amounts that the product of their concentration in mg. per 100 c.c. serum equals a certain minimal figure which ranges between 30 and 40. In rickets they found that the concentration of calcium in the majority of instances is essentially normal whereas the phosphorus concentration is definitely low.

Hess and Unger,[63] however, state that a low inorganic phosphorus does not indicate whether the rachitic process

is healing or advancing, since they have met with examples where radiological examination revealed healing although the inorganic phosphorus had increased but little from the previous low figure found during the active phase. These authors considered that the most valuable criterion of healing was the radiogram. A year later Hess, Calvin, Wang and Felcher (64) concluded that consecutive blood examinations are of greater importance than radiographic evidence in the determination of the stage of rickets.

In the present investigation the behaviour of the inorganic phosphorus of the serum was studied in order to determine the relative value of (1) a single observation and (2) a series of observations. The observations were controlled by X-ray findings.

Single observations were made in 27 cases which have been classified according to the radiological appearances into 3 groups. Group I includes 7 cases of rickets in which radiograms taken at weekly intervals over a period of 3 weeks showed no evidence of healing. In Group II are included 8 cases in which the observations were made at the time when the first appearance of healing radiologically declared itself and in Group III are 12 cases in which radiographic evidence of healing had been in progress for at least 2 weeks. In all of these cases the serum calcium was normal.

In Group I (active rickets) the inorganic phosphorus of the serum varied between 2.1 mg. and 3.8 mg.% with an average of 2.9 mg. In Group II (early healing) the serum phosphorus varied between 2.5 mg. and 5.0 mg.% the average value being 3.9 and in Group III (more advanced healing) the serum phosphorus was still definitely higher varying between 3.8 and 6.5 mg.% with an average of 5.0. (Table XXIV).

TABLE XXIV.

Single Observations on Serum Phosphorus in Rickets.

Stage of Disease.	No. of Cases.	Inorganic Phosphorus of Serum.		
		Maximum value mg.%	Minimum value mg.%	Average value mg.%
Active.	7	3.8	2.1	2.9
Early Healing.	8	5.8	2.5	3.9
More Advanced Healing.	12	6.5	3.8	5.0

Table XXV shows the products of the calcium and inorganic phosphorus contents of the serum in the 3 groups of cases.

TABLE XXV.

Products of the Calcium and Inorganic Phosphorus Content of the Serum in Rickets.

Stage of Disease.	No. of Cases.	Product of Calcium & Phosphorus of Serum.		
		Maximum	Minimum	Average.
Active.	7	36	22	28
Early Healing.	6	60	24	38
More Advanced Healing.	11	68	38	52

CHART XIV

Inorganic phosphorus content of serum in three cases of rickets before and during treatment.

// commencement of healing.

X first appearance of healing in radiograms.

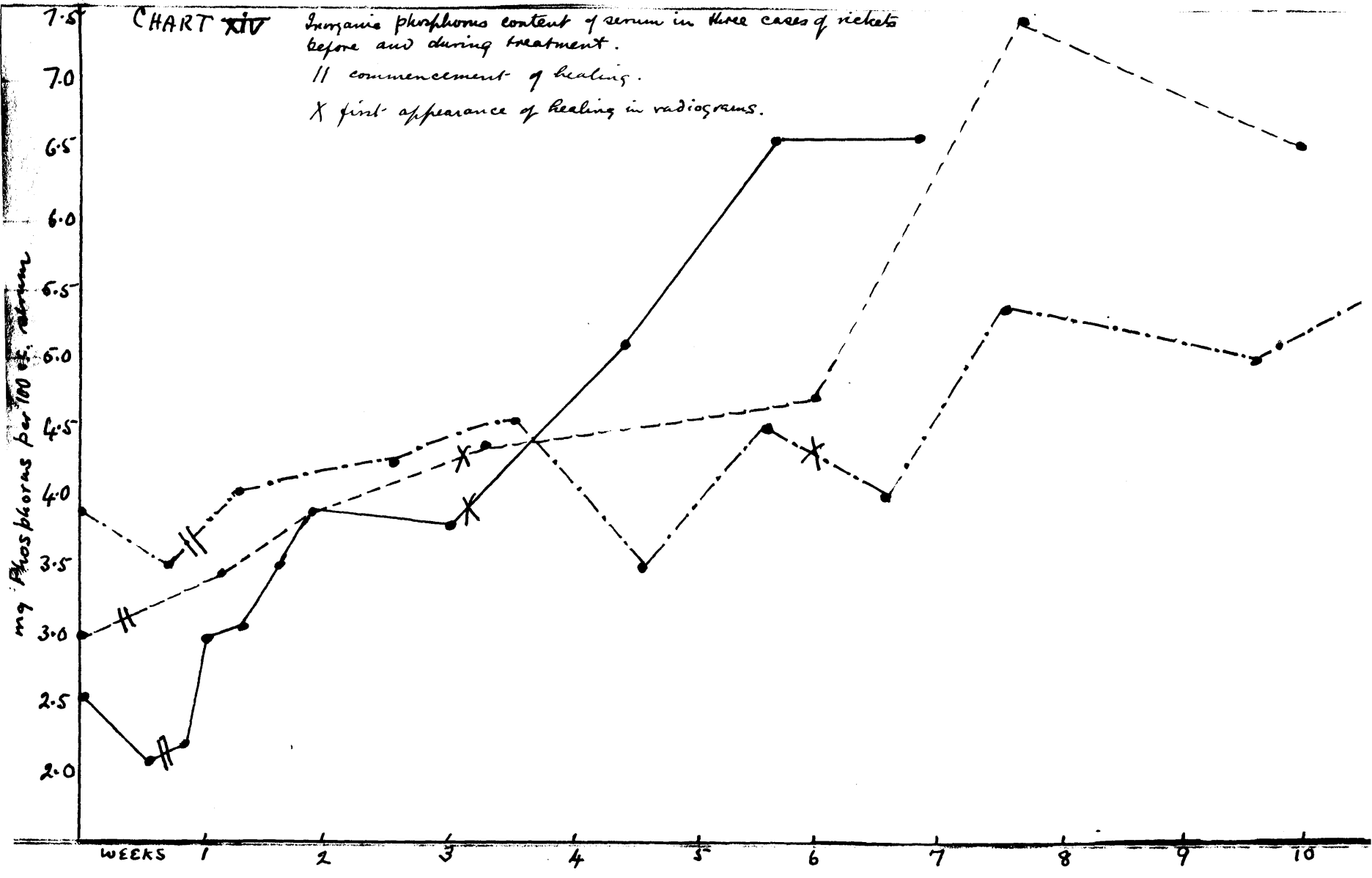


CHART ~~XV~~

Inorganic phosphorus content of serum in two cases of rickets before and during treatment.

// Commencement of treatment.

X First appearance of healing in radiograms.

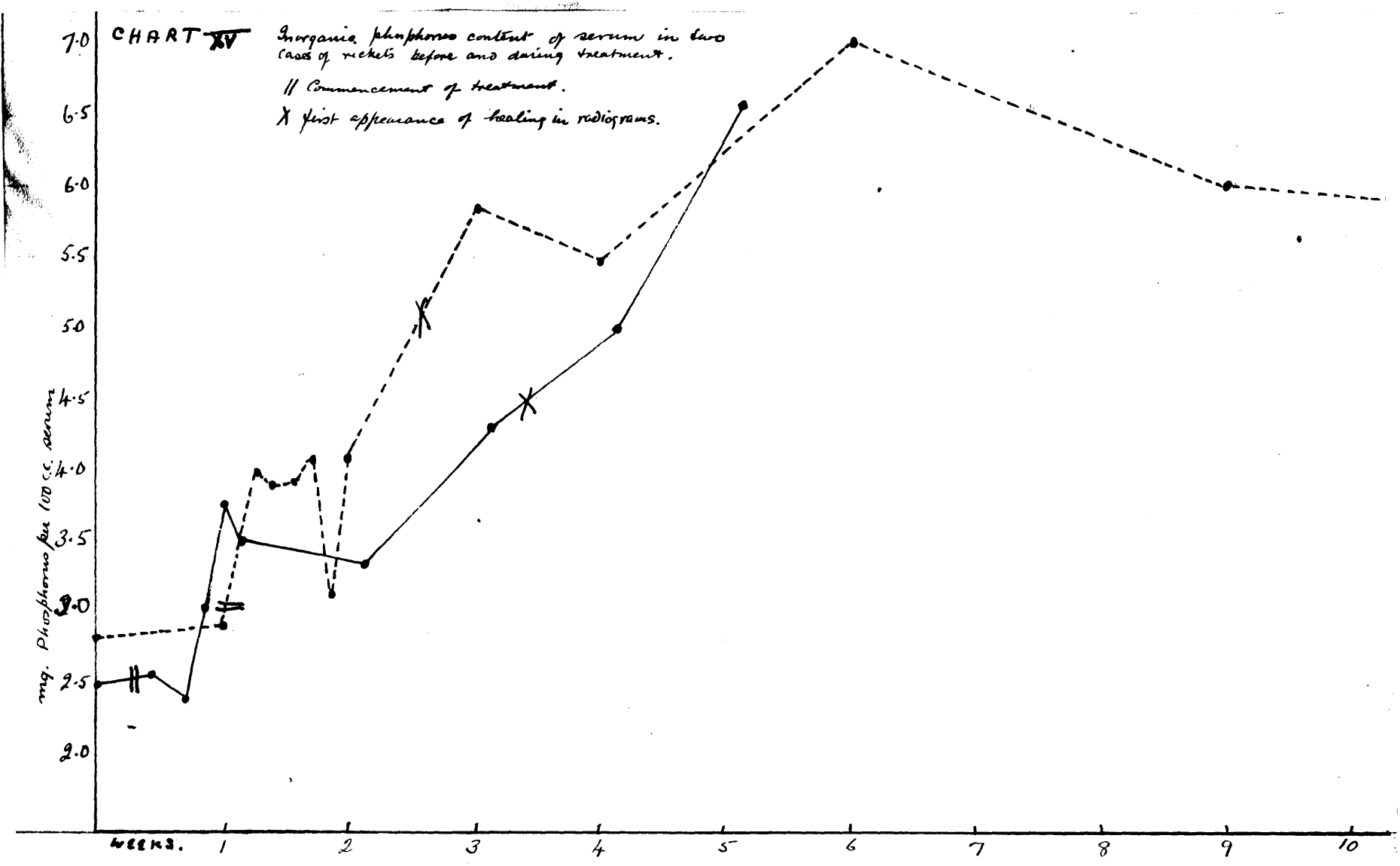
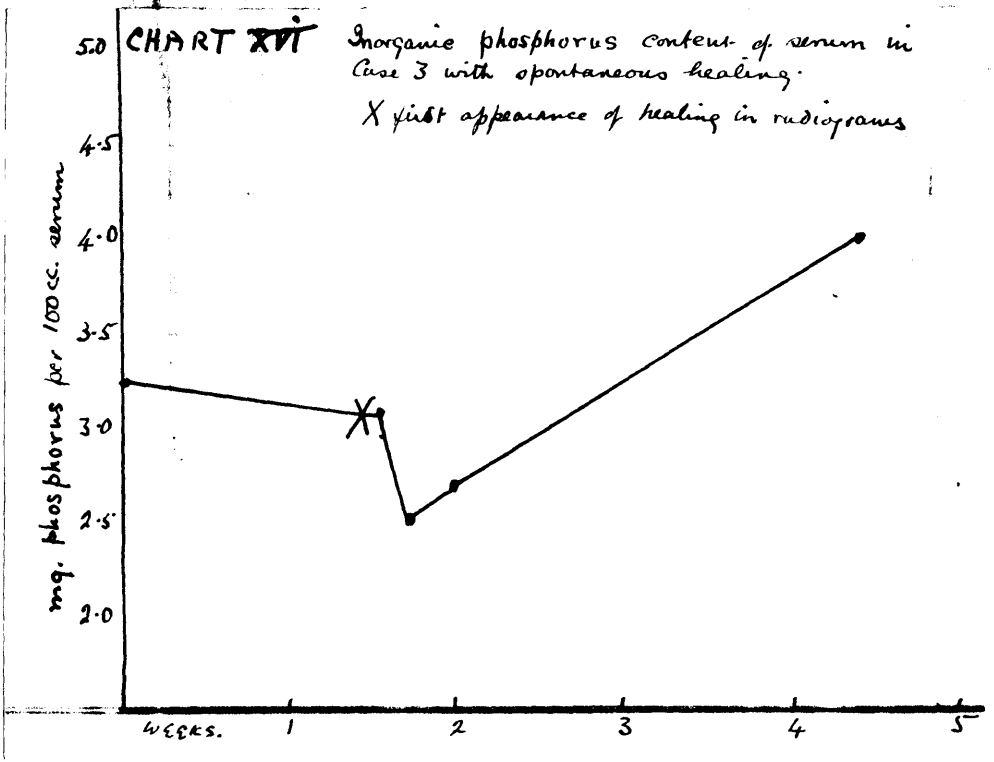


CHART XVI

Inorganic phosphorus content of serum in Case 3 with spontaneous healing.

X first appearance of healing in radiograms



In Group I this product varied between 22 and 36 the average being 28, in Group II it varied between 24 and 60 with an average of 38 and in Group III between 38 and 68 with an average of 52.

In each of 6 cases of rickets a series of observations on the serum phosphorus was obtained during the active and healing phases. In one patient in this group healing commenced spontaneously but in each of the other 5 healing was induced by one or other of the recognised forms of treatment. In the treated cases (Charts XIV and XV) the general level of the serum phosphorus rose before radiological examination revealed healing. Subsequent to the appearance of healing in the radiographic picture the serum phosphorus however showed a further and more marked increase. In the case of spontaneously healing rickets (Chart XVI) the inorganic phosphorus of the serum fell from 3.4 mg. to 2.5 mg.% over a period of 2 weeks during which time progressive healing was apparent in the successive X-ray pictures.

Discussion.

(1) Isolated Observations: A study of the results of the isolated determinations of the serum phosphorus shows quite clearly that the average values in active, slightly healing and more advanced healing rickets are

in ascending order. It is, however, equally noteworthy that there is a very marked overlapping of the figures of these groups, the value 3.8 mg.% being common to all three. One must therefore conclude that an isolated observation of the serum phosphorus cannot be taken as an unequivocal index of the stage of the disease.

(2) Product of the calcium and phosphorus contents of the serum: It will be noted that in all the cases of active rickets the product of the calcium and inorganic phosphorus contents of the blood serum is below the upper limit of 40 described by Howland and Kramer (62) for active rickets. That this limit, however, is of no practical value for determining the activity of the disease is shown by the fact that 3 (50%) of the cases of early healing and 1 (9%) of these presenting more advanced healing also showed products below this limit.

(3) Serial Observations: As can be seen from Charts XIV, XV, and XVI the serum phosphorus rises as healing progresses in all cases except J.P. (Chart XVI). In this last patient early healing as indicated by radiograms is accompanied by a slight fall in the serum phosphorus value, but it should be noted that this is the only patient in whom a series of observations was obtained during spontaneous healing and therefore one is loth to draw far-reaching conclusions.

In the other patients in all of whom healing followed some definite course of treatment, the value for the serum phosphorus showed a considerable increase prior to the appearance of X-ray evidence of healing. This increase exceeded in 3 cases the maximum value obtained in admittedly active rickets, and in the other 2 cases reached the upper limit of the values obtained in the active group. The question arises as to the significance of this rise, and it might be suggested that it should be taken as evidence of healing occurring previous to the appearance of a positive X-ray finding. In support of this view is the fact that on the whole the rise in serum phosphorus once commenced is fairly steady. There are, however, occasional falls but the main tendency of the graphs is upward. One would naturally expect that such a rise would occur before increased calcification of the bones could be detected radiographically and it is probable that a steady rise in the value for serum phosphorus is evidence of healing despite the absence of positive X-ray findings.

B. The Metabolism of Calcium and Phosphorus.

That there is a diminution in the retention of lime in active rickets is well recognised. Schabad (7) in 1910 found a very low calcium retention in early rickets, in

fact in some instances more lime was excreted than was ingested. In cases of longer duration he found that the retention returns to normal or is increased above the normal before any clinical signs of recovery are apparent. With the lowering of the retention of lime there occurs a corresponding decrease in the retention of phosphoric acid due to an increased elimination of P_2O_5 in the faeces. Some years later Findlay, Paton and Sharpe (12) in studies of the calcium metabolism in rickets found an increased excretion of lime during the active stage but in no instance did they obtain a negative balance, i.e. more excreted than ingested. These authors pointed out for the first time that the metabolic picture differs according to the activity or non-activity of the disease and not according to its duration. Five years later Telfer, (10) confirming their findings, drew attention to the difference in the mode of excretion of P_2O_5 in the active and healing phases. He showed that during the active period the greater part of the phosphorus is excreted in the faeces while during the healing stage the urine contains the larger amount. Thus in active rickets the ratio $\frac{P_2O_5 \text{ in the urine}}{P_2O_5 \text{ in faeces}}$ is less than 1 while during healing it is much greater than unity.

The metabolism studies forming the basis of this

TABLE XXVI.

Metabolism of Calcium and Phosphorus in Active Rickets. Treated Rickets, and Spontaneously Healing Rickets.

Case No.	X-ray findings before Metabolism Study.	X-ray findings after Metabolism Study.	Treatment.	CaO in Urine. % Total output.	Ratio P_2O_5 in Urine / P_2O_5 in faeces	Daily Retention per kilo body weight. CaO gm.	Daily Retention per kilo body weight. P O gm.
1.D.D.	Active	Active	nil.	0.3%	1/2.7	0.04	0.04
2.D.B.	active	active	nil.	0.4%	1/1.6	0.04	0.04
1.D.D.	active	healing	Irradiation	3.7%	4.7/1	0.25	0.22
2.D.B.	active	healing	Radiostol.	2.6%	4.4/1	0.10	0.08
3.J.P.	active	slight healing	nil.	0.4%	2/1	0.07	0.07
4.H.W.	? healing.	definite healing	nil.	0.8%	1/3.1	0.05	0.08
5.D.B.	healing	further healing	nil.	1.9%	2.4/1	0.13	0.13

investigation were made in cases of active rickets, in cases of spontaneously healing rickets and in examples of rickets where healing had been induced by treatment. The three groups comprise in all 5 cases. Two observations were obtained in patients during the active stage of the disease, 3 observations during a spontaneously healing phase, and 2 observations during a period of healing induced by treatment. These studies were carried out in a similar way to the balance experiments already described.

The results are given in Table XXVI.

The following is a brief description of the cases. Case 1, D.D., aet $^{7}/_{12}$ years was kept under observation for 3 weeks during which period radiographic examination showed no evidence of healing. A metabolism study was then made. The daily retentions of CaO and P_2O_5 were each .04 gm. per kilo body weight, the urinary excretion of lime was 0.3% of the total output, and the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ was $\frac{1}{2.7}$. At the end of that period the patient was given daily exposures to radiations from a mercury vapour quartz lamp and during the second week of this treatment the daily retentions of CaO and P_2O_5 were found to have increased respectively to 0.25 gm. and 0.22 gm. per kilo body weight. The output of lime

in the urine increased to 3.7% of the total output and the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ became $^{4.7}/_{1}$. Healing was first noted radiographically at the end of this period, that is, the end of the second week on treatment.

Case 2, D.B., aet $^{6}/_{12}$ years. For 4 weeks there was no evidence of healing in the radiograms. The daily retentions of CaO and P_2O_5 were each .04 gm. per kilo body weight. Radiostol m.IV 3 times daily was then given. During the second week of treatment the daily retentions of CaO and P_2O_5 were increased respectively to 0.10 and 0.08 gm. per kilo body weight. The urinary output of lime increased from .4% to 2.6% of the total output and the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ which was $^{1}/_{1.6}$ during the first period, became $^{4.4}/_{1}$.

Case 3, J.P., aet 1 $^{5}/_{12}$ years. Weekly radiograms were taken for a period of 3 weeks before patient was admitted to hospital. There being no evidence of healing the child was admitted to hospital and a metabolic study carried out which showed that the daily retentions of CaO and of P_2O_5 were each .07 gm. per kilo body weight. The urinary output of CaO was 6.4% of the total output and the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ was $^{2}/_{1}$. A radiogram at the end of this period showed definite healing.

Case 4, H.W., aet 1 $^{10}/_{12}$ years. Radiograms taken for 4 weeks before admission to hospital showed no evidence of

healing. The patient was then admitted to hospital and at the end of 2 weeks residence in the ward a suspicion of healing was noted in the radiographic picture. A metabolism study made at this time showed that the daily retentions of CaO and P_2O_5 were respectively .05 gm. and .08 gm. per kilo body weight. The urinary output of lime was 0.8% of the total output and the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ was 1/3.1. Radiogram taken at the end of this period showed definite healing.

Case 5, D.B., aet 3 10/12 years. For 3 weeks before admission there was no radiographic evidence of healing. After 1 week in the ward slight healing was noted. During the second week in hospital a metabolic study was made. The daily retentions of CaO and P_2O_5 were each 0.13 gm. per kilo body weight. The output of CaO in the urine was 1.9% of the total output, the ratio $\frac{P_2O_5 \text{ in urine}}{P_2O_5 \text{ in faeces}}$ was 2.4/1. Further healing was noted in the radiogram taken at the end of the study.

Of the cases recorded above the retentions of CaO and P_2O_5 in the 2 patients where the metabolism studies were made during the active stage of the disease were low, the urinary output of lime was very low and the greater proportion of the phosphorus was eliminated in the faeces. After seven days' treatment by irradiation or the administration of radiostol there resulted

a marked increase in the retentions of both CaO and P_2O_5. The urinary output of lime was also increased and the large proportion of phosphorus left *via* the kidneys.

Of the 3 examples of spontaneously healing rickets Case 3, where the first radiographic evidence of healing was noted at the end of the metabolic study, had a low but normal retention of CaO and P_2O_5 while Case 5, where the first radiographic evidence of healing was noted before the metabolic study commenced had a retention of CaO and P_2O_5 exceeding the upper limit of normality. Only the latter case which showed the most advanced healing presented a normal % output of lime in the urine. In the other 2 cases the urinary output of lime resembled that met with during the active stage of the disease. It will thus be seen that the retention of lime increases from a low normal retention in the case of earliest healing to a retention slightly above normal in the case of more advanced healing. It would appear probable from these results that in spontaneous healing a slight increase occurs in the retentions of CaO and P_2O_5 before radiological evidence of healing and that with the advance of healing noted in the radiographic picture a further gradual increase occurs.

It is interesting to contrast the results obtained in spontaneously healing rickets with those obtained in the treated cases. In the treated cases there occurred a marked increase in the retentions of CaO and P_2O_5 during the week preceeding the first radiographic appearance of healing. The increase in the urinary output of lime was more marked in the treated cases as was also the change in the mode of excretion of P_2O_5. This early marked change in the mineral metabolism in treated cases is comparable to the increase noted in the serum phosphorus in treated rickets before X-ray evidence of healing and is probably to be attributed to the greater rapidity with which healing takes place when efficient treatment is given.

Conclusions.

1. Isolated observations on the inorganic phosphorus content of the blood serum are of no practical value in determining the phase of the disease because figures obtained from such observations in early healing often fall within the limits of those of the active stage. The same objection applies to the use of the figure representing the product of the phosphorus and calcium contents (mg. per 100 c.c.).

2. Serial observations on the serum phosphorus over a period of 2 to 3 weeks are of assistance only when the

disease is healing rapidly as e.g. when active treatment is being employed.

3. A determination of the calcium balance is the most reliable means of arriving at a decision. The objection to this method is the time and labour involved, as after the metabolic study which extends over 7 days is finished, a further week or 10 days is required before the necessary analyses can be completed.

4. Radiograms taken over a period of 3 weeks are on the whole a fairly reliable means of determining the phase of the disorder, and they involve much less trouble, though they may fail to show such an early stage of healing as the calcium balance estimations do.

5. Whichever method is used a period of about 3 weeks is necessary to arrive at a satisfactory decision. Also it is to be remembered that if the 3 weeks observations are made while the case is an out-patient the results of these observations may indicate an active stage and yet because of change in environment healing may be evident very shortly after the patient is admitted to hospital for investigation of the value of treatment. This happened in 3 of the cases recorded above. It is therefore essential that the observations be made while the patient is in the ward where all conditions can be controlled.

Part II: The Value of Different Therapeutic Agents in the Treatment of Rickets.

Within recent years great advances have been made in our knowledge of the exciting factor in the production of rickets and as a consequence of this many new methods of treating the disease have been introduced. The widespread incidence of rickets makes an investigation of the value of the different forms of treatment a matter of great practical importance. The object of this investigation is to demonstrate the relative value of some of these different methods by a comparative study of their influence on the radiological picture, tne Ca and P content of the blood, and the retentions of Ca and P.

Although the absence of sunlight as a cause of rickets was suggested by Huntly (65) as long ago as 1889 it was not until 1919 that, in consequence of the work of Huldschinsky (66) definite evidence was brought forward. This author was successful in effecting cure by exposure of the body to ultra-violet rays emanating from a Hg-vapour quartz lamp. Since then many workers have published their results with this therapeutic measure and it is now generally accepted that the length of time which elapses before healing becomes apparent in radiograms is from 2 to 5 weeks. Chick (67) in Vienna noted healing in from 2 to 4 weeks after commencement of irradiation and Carter Braine and Osman (68) report cases

in which healing appeared after 2 to 5 weeks of ultra-violet ray therapy. In a series of 5 cases Kramer, Casparis and Howland (69) reported the effect of irradiation on the X-ray picture and the blood serum findings. They noted that healing became evident within 4 weeks from commencement of treatment and that the inorganic phosphorus content of the blood rose from 3 mg. to 6 mg. per 100 c.c. serum in 6 to 11 weeks.

Fewer cases have been reported in which the retention of lime has been studied. In 1921 Meyer (70) contrasted the effect of cod liver oil and that of ultra-violet light on craniotabes and concluded that ultra-violet light was equal, or even superior to cod liver oil. In 2 cases he found a considerable increase in the retention of lime during ultra-violet light treatment. Orr, Holt, Wilkins and Boone (71) have also reported an increase in the retentions of CaO and P_2O_5 in cases of infantile rickets treated with ultra-violet light.

Although there have been many reports on the effect of administration of various preparations of irradiated ergosterol on the course of rickets so far no observations have been published on the effect of this substance in therapeutic doses on the retention of CaO and P_2O_5. Karelitz, (72) giving vigantol in doses equivalent to 3.3 mg.

irradiated ergosterol daily, found healing in the radiographic picture as early as 7 days, the average time of the first appearance of healing however being 21 days from commencement of treatment, and the inorganic phosphorus content of the serum rising to normal in 14 to 21 days. Györgi,[73] Vollmer[74] and other German workers using the same substance - vigantol - have reported similar results. In a series of 5 cases treated with radiostol Aidin[75] found the earliest radiological evidence of healing in from 3 to 8 weeks.

In the present investigation different methods of treatment were studied in 14 cases of active rickets. The course of the disease was followed in all cases in weekly radiograms for at least 3 weeks prior to commencement of treatment, and with 2 exceptions, the patients were in hospital during the entire period of observation. The effect of treatment was noted (1) on the calcification of the bones as seen on radiological examination, (2) on the calcium and inorganic phosphorus contents of the blood serum, and (3) on the retentions of CaO and P_2O_5.

In all cases in which it was possible a metabolism study was made before treatment and during the second week of treatment. Each metabolic study as in the case of the balance experiments already described extended over a period of 7 days, the diet being constant for at least 3

days prior to the actual metabolic investigation.

The cases are divided into 4 groups according to the method of treatment employed:

Group I consists of 5 cases who received direct irradiation of the skin. Of these, 3 were examples of ordinary infantile rickets, the other 2 being older children, one a boy aged 9½ years and the other a girl aged 12 years. The boy (Case 4, D.M.) was admitted to hospital on account of difficulty in walking: he had first started to walk at the age of 3 years but always tired quickly and tended to fall: from the age of 6 years till the date of admission the condition became worse: on admission he appeared small (12 cm. below average height) but well nourished with epiphyseal enlargement and marked genuvalgum. In the case of the girl it was noted that prior to admission the knee had been "turned in" for one year during the last month of which she dragged the right leg in walking: she was a fair sized girl with a slight degree of genu valgum. In both these cases radiological examination showed a fairly marked degree of active rachitic change.

Treatment was begun by exposing the back for 2 minutes to radiations from a Hg-vapour quartz lamp at a distance of 4 ft. The exposures were increased daily according to the tolerance of the skin.

Group II includes 4 examples of infantile rickets treated with radiostol. Three of the children received 4 mm. of a solution of radiostol in oil 3 times daily and 1, who was an outpatient (Case 9, M.M.) was given 2 radiostol pellets daily.

In Group III are 3 cases (1 of which, Case 10, A.P.) was an outpatient) treated with 2 pellets of vigantol daily (1 pellet - 4 mg. irrad. ergosterol) while Group IV includes 2 cases treated with ℥ss cod liver oil 3 times daily.

The results are summarised in Table XXVII.

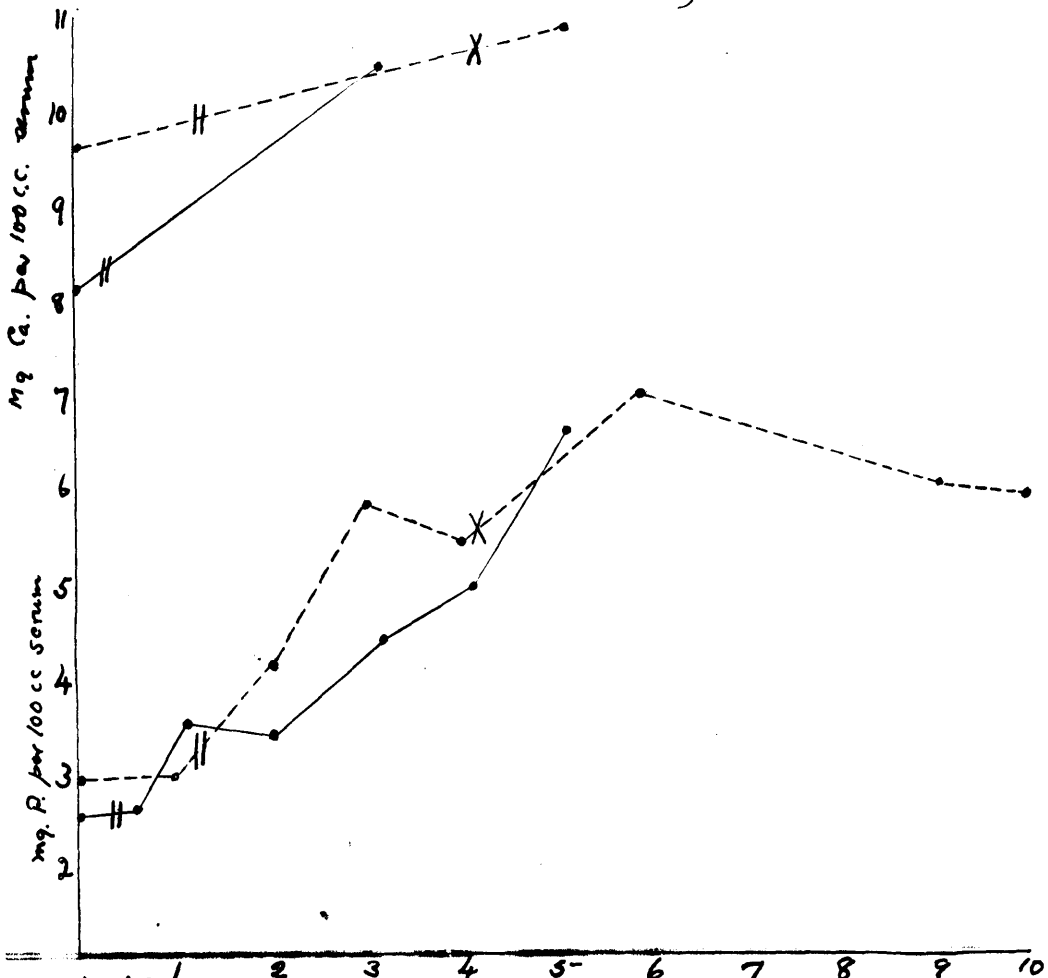
TABLE XXVII.

Showing effect of different forms of treatment on radiograms, serological findings and mineral retention.

Case	Age years	Treatment	Radiographic Findings		Blood Chemistry findings				Daily Retention per Kilo.			
			First appearance of healing.	Subsequent rate of healing.	Before Treatment		End of 2nd week of Treatment		Before Treatment		End of 2nd week of Treatment	
					Serum Ca mg.%	Serum P mg.%	Serum Ca mg.%	Serum P mg.%	CO_2 gm	PO_4 gm	CO_2 gm	PO_4 gm.
1. M.C.	1 9/12	Irradiation	3 weeks	Rapid	8.13	2.5	10.47	4.3				
2. M.L.	2 5/12	"	12 days	"	9.56	2.8	-	5.8				
3. D.D.	2 7/12	"	2 weeks	"	7.29	4.3	10.09	4.3	+.039	+.045	+.255	+.220
4. D.M.	9	"	2 weeks	"	-	4.1	-	6.4	-.003	+.004	+.10	+.08
5. M.O'N	12	"	4 weeks	slow	11.2	3.0	11.08	5.2	+.03	+.02	+.08	+.08
6. D.M.	11/12	Radiostol	4½ weeks	slow	-	3.4	-	4.0				
7. D.B.	1 1/2	"	2 weeks	Rapid	8.46	4.0	9.9	5.1	+.042	+.043	+.104	+.080
8. W.K.	3½	"	3 weeks	slow	10.04	3.0	-	4.4				
9. M.M. (o.p)	3	"	5½ weeks	slow	8.6	3.1	9.2	3.7 (7½ wks.)				
10. A.P. (o.p)	2½	Vigantol	2 weeks	Rapid	9.2	2.0	9.4	4.1				
11. J.K.	1 1/2	"	1 week	Rapid	5.1	7.1	8.1	4.4				
12. J.C.	1½	"	1 week	slow	4.0	4.8	10.2	9.2 (3 wks)	+.027	+.037	+.124	+.097
13. J.B.	2	Cod Liver Oil	17 days	Rapid	10.04	3.0	-	4.0				
14. J.P.	2	"	18 days	Rapid	8.5	2.1	8.84	3.33	+.039	+.048	+.153	+.156

CHART XVII Treatment with ULTRA-VIOLET LIGHT.
|| indicates onset of treatment.
X " cessation of treatment.

CASE 1. M.C. ——
CASE 2. M.L. (Cirhosis + Acute tetany) - - - - -



CASE 4 D. M. ——
CASE 5 M. O'N. - - - - -

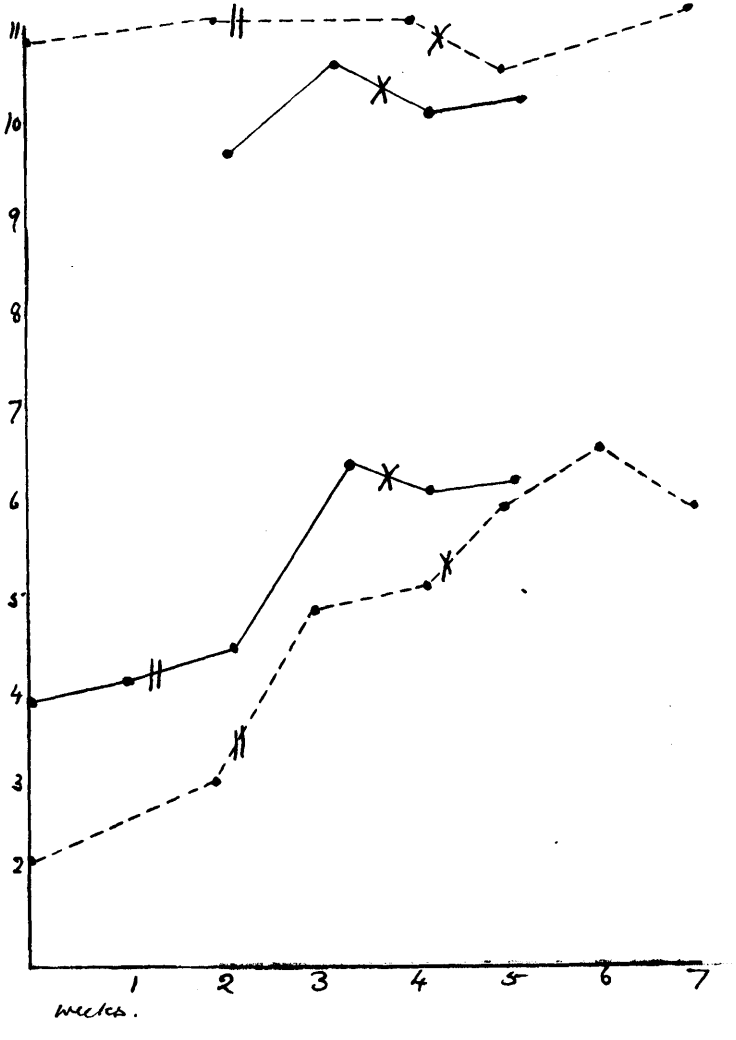
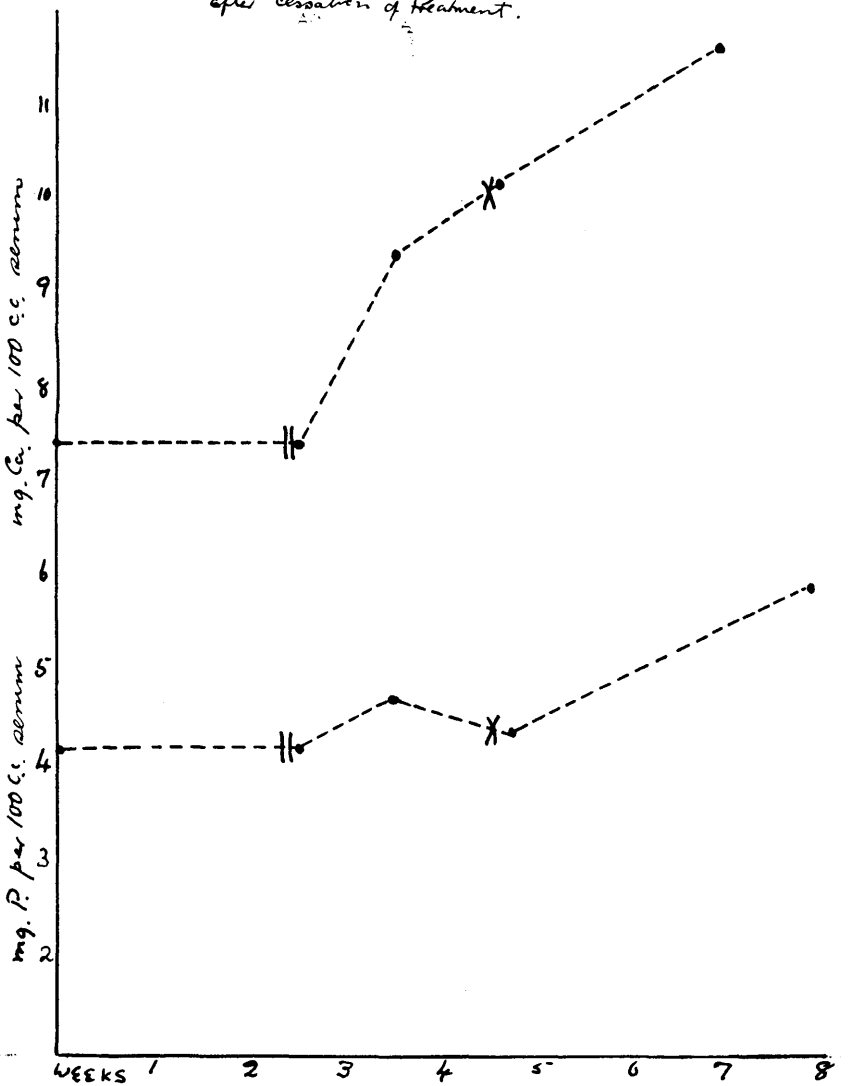


CHART XVIII Treatment with Ultra-violet light.

Case 3 D.D. (rickets + Potent tetany) showing continued improvement after cessation of treatment.



1. Radiological Findings.

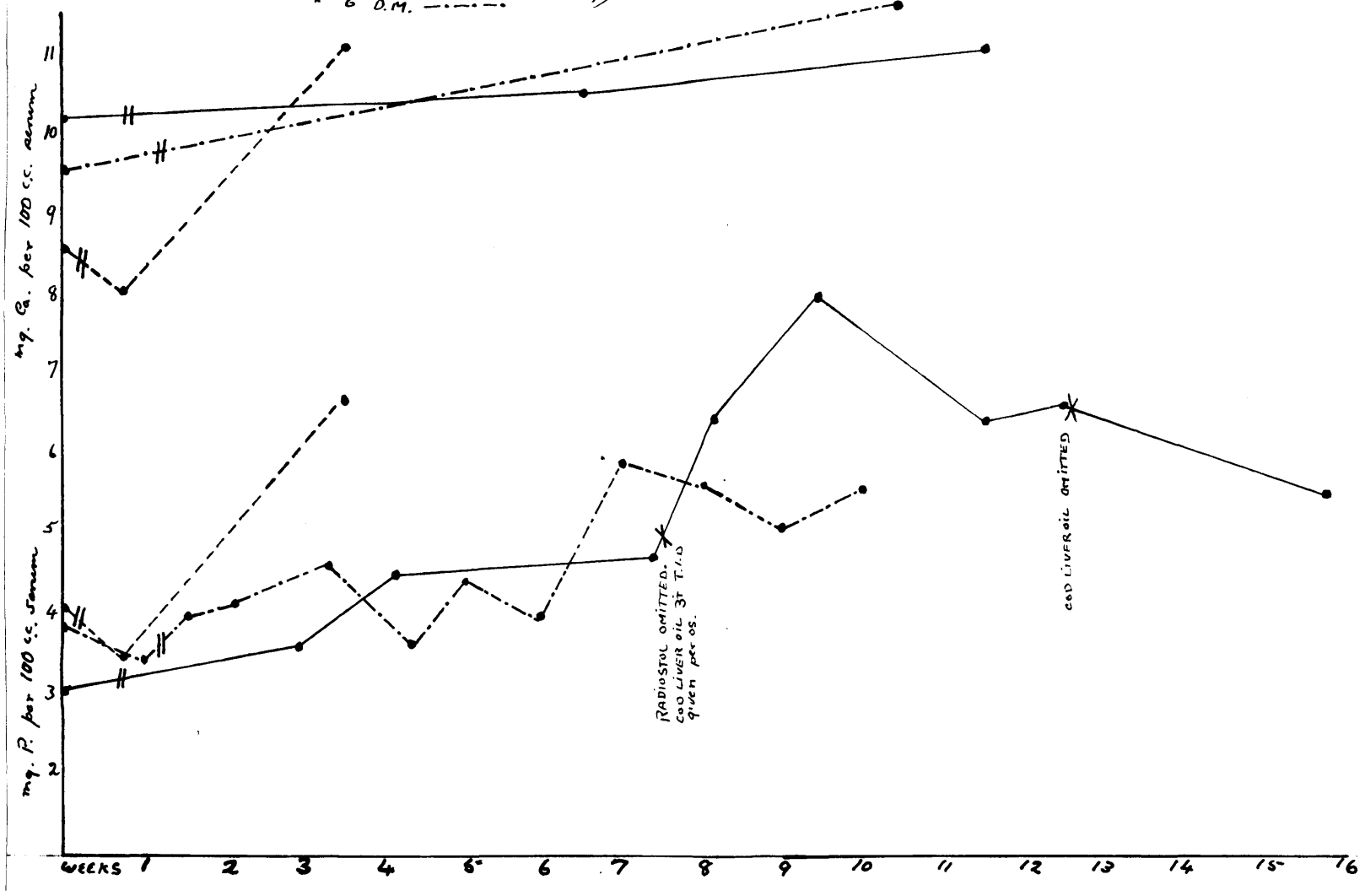
In the group of cases treated with irradiation the time between the commencement of treatment and the first appearance of healing noted on X-ray examination varied from 12 days to 4 weeks. Taking the cases of infantile rickets only, it varied from 12 days to 3 weeks. With the use of cod liver oil healing became evident in $2\frac{1}{2}$ weeks and with vigantol in 1 to 2 weeks. In the cases treated with radiostol this period was somewhat longer varying from 2 weeks to $5\frac{1}{2}$ weeks, the average being $3\frac{3}{4}$ weeks (Table XXVII). The subsequent rate of healing as judged from radiological evidence was, on the whole, slower in those cases treated with radiostol than in the patients who received the other forms of treatment.

2. Changes in Serum Ca and P.

Group I. The behaviour of the serum Ca and P in the group of cases treated with ultra violet light is shown in Charts XVII and XVIII. Two of these cases (Case 1, M.C., and Case 3, D.D.) were complicated by latent tetany and in both the serum Ca rapidly rose to normal after 1 to 3 weeks of treatment. In 4 of the cases the initial level of the serum P was low, varying from 2.1 mg. to 3.9 mg. and rose to a maximum of from 6.5 mg. to 7 mg.

CHART. XIX TREATMENT WITH RADIOSTOL.
// indicates onset of treatment.

CASE 8 W. K. ——
" 7 D. B. (rickets + Latent tetany) – – – –
" 6 D. M. —·—·—·



in 2½ to 6 weeks. Chart XVIII illustrates the continued improvement in Case 3, D.D. after the cessation of treatment.

Group II. In the cases treated with radiostol the blood changes were not so marked (Chart XIX). In Case 6, D.M. who had an initial normal serum calcium of 9.49 mg. per 100 c.c. and a serum phosphorus of 3.4 mg., the rise in the serum P to a maximum of 5.8 occurred in 6½ weeks. In Case 8, W.K. who also had a normal serum Ca the phosphorus had not risen above 4.7 mg. at the end of 6 weeks of treatment. Administration of radiostol was then omitted and cod liver oil in ℥ doses given 3 times daily. The serum P rose rapidly reaching a height of 8 mg. in 2 weeks, thereafter showing a gradual fall. In Case 9, M.M. who was treated as an outpatient, it took 7½ weeks for the serum P to rise from 3.1 mg. to 3.7 mg. and the serum Ca to rise from 8.6 to 9.2 mg. (Table XXVII). In Case 7, D.B. who had had an initial serum Ca of 8.5 mg. and serum P of 4.0 mg. the values of both rose rapidly to 11.1 mg. and 6.1 mg. respectively after 3 weeks treatment.

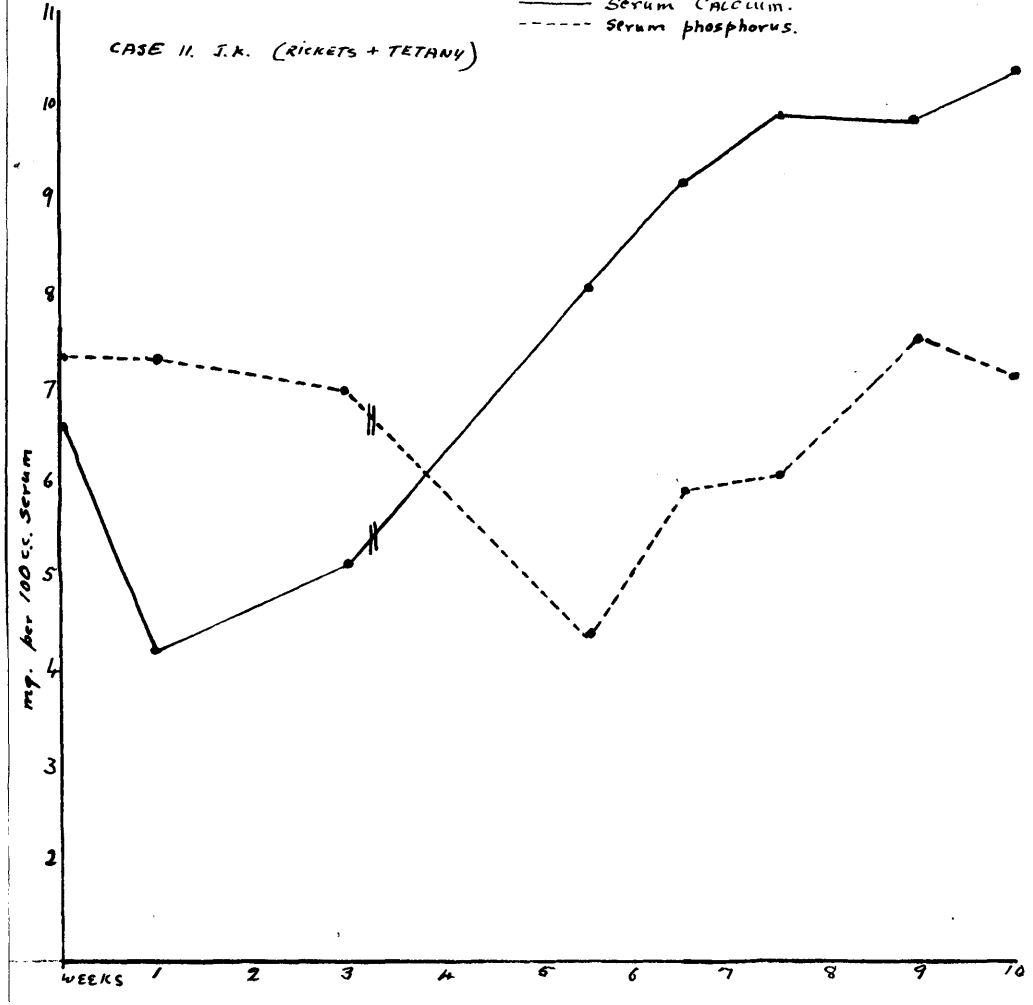
Group III. In the 2 inpatients who were treated with vigantol Chvostek's sign was present and both had laryngismus. The serum Ca was very low, being 5.1 mg. in Case 11, J.K. and 4.0 in Case 12, J.C. After 3 weeks

CHART ~~XX~~ TREATMENT WITH VIGANTOL.

// Indicates onset of treatment.

——— Serum Calcium.

------ Serum phosphorus.



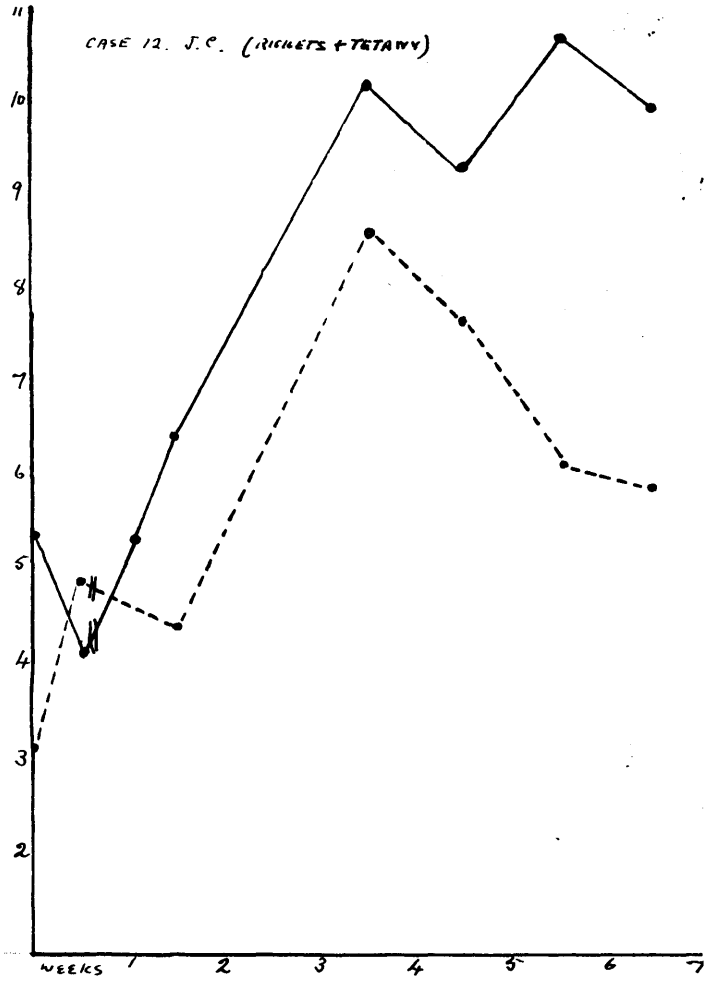


CHART ~~XXI~~ Treatment with cod liver oil
// indicates onset of treatment

Case 13 J.B. ——
Case 14 J.P. (rickets + latent tetany) ------

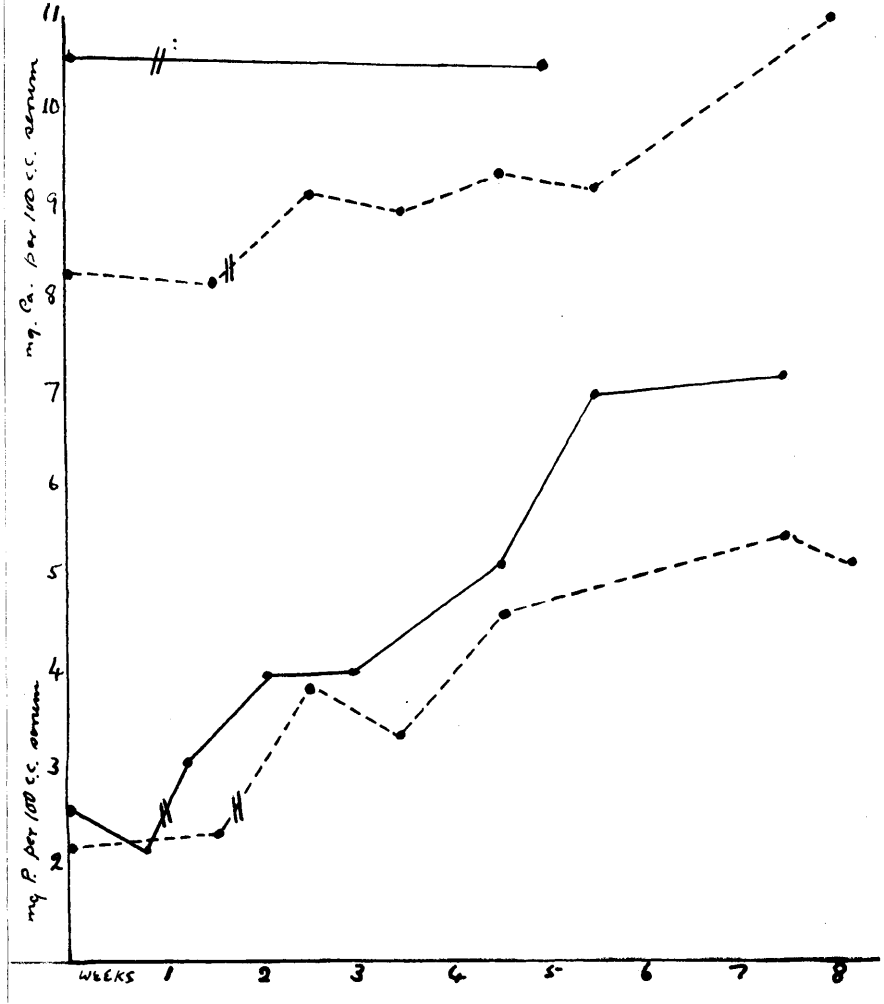


TABLE XXVIII

Metabolism of CaO and P_2O_5 in 4 cases of infantile rickets before and during 2nd week of Treatment.

Case	Age years	Period	Total Intake CaO gm.	Total Intake P_2O_5 gm.	Total Output CaO gm.	Total Output P_2O_5 gm.	Faecal output CaO gm.	Faecal output P_2O_5 gm.	Urine output CaO gm.	Urine output P_2O_5 gm.	Ratio Ur P_2O_5 / Faec. P_2O_5	Total Retention CaO gm.	Total Retention P_2O_5 gm.	Daily Retention per Kilo CaO gm.	Daily Retention per Kilo P_2O_5 gm.
Case 3	2 7/12	Before Treatment.	16.632	21.672	14.336	18.993	14.286	13.823	.050	5.17	1/2.7	2.296	2.679	.039	.045
		During Irradiation	16.632	21.672	2.204	9.201	2.121	1.606	.083	7.595	4.7/1	4.428	12.471	.255	.220
Case 7	6/12	Before Treatment.	11.157	15.592	9.082	13.473	9.047	8.293	.035	5.18	1/1.6	2.075	2.119	.042	.043
		During Administration of Radiostol	11.157	15.592	5.926	11.557	5.771	2.137	.155	9.42	4.4/1	5.231	4.035	.104	.080
Case 12	1 6/12	Before Treatment.	12.60	17.64	10.869	15.331	10.693	10.613	.176	4.718	1/2.2	1.731	2.309	.027	.037
		During ad. of Vigantol	12.60	17.64	4.82	11.551	4.60	1.807	.220	9.744	5.3/1	7.78	6.091	.124	.097
Case 14	2 7/12	Before Treatment.	11.76	16.17	9.848	13.849	9.753	10.721	.095	3.128	1/3.4	1.912	2.321	.039	.048
		During ad. of Cod liver Oil	11.76	16.17	4.356	8.735	4.272	3.126	.084	5.609	1.8/1	7.404	7.435	.153	.156

treatment the value for the serum Ca rose in the former to 9.1 mg. and in the latter to 10.2 mg. (Chart XX). In Case 10, A.P. who was treated as an outpatient the initial serum Ca was normal. The serum P which was 2.0 mg. before treatment rose to 4.1 mg. in 2 weeks (Table XXVII).

Group IV. Of the 2 children treated with cod liver oil one (Case 14, J.P.) had latent tetany, the serum Ca being 8.5 mg. During the first 4 weeks of treatment this figure varied between 8.8 mg. to 9.2 mg. and then rose to 10.8 at the end of $7\frac{1}{2}$ weeks while the value for the serum P showed a gradual increase from 2.1 mg. to 5.4 mg. In the other patient (Case 13, J.B.) whose serum Ca was normal, the serum P showed a more rapid increase, reaching a maximum of 7 mg. in $6\frac{1}{2}$ weeks (Chart XXI).

From these results it will be seen that the blood changes produced by the different methods of treatment were very similar although with the use of radiostol the increase in serum P was somewhat less marked.

3. Metabolism Studies.

A study of the Ca and P metabolism was obtained in one case of infantile rickets from each of the 4 groups. The results are shown in Table XXVIII. In all the cases

TABLE XXIX.

Metabolism of CaO and P_2O_5 in 2 older children before and during 2nd week of treatment.

Case	Age	Period	Total Intake		Total Output		Faecal output		Urine output		Ratio Ur. P_2O_5 / faec P_2O_5	Total Retention		Daily Retention per kilo	
			CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5		CaO	P_2O_5	CaO	P_2O_5
			gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.		gm.	gm.	gm.	gm.
Case 4	9yr	Before Treat.	16.80	23.10	17.362	22.507	17.293	12.006	.069	10.501	1/1.14	-.56	+.593	-.003	+.002
		During Irrad.	16.80	23.10	2.776	11.798	2.673	1.803	.103	9.995	5.5/1	14.024	11.302	.099	.080
Case 5	12½yr.	Before Treat.	20.16	27.72	14.719	23.573	14.431	13.97	.288	9.603	1/1.4	5.441	4.15	.029	.022
		During Irrad.	20.16	27.72	6.073	13.801	4.753	4.332	1.32	9.469	2.2/1	14.087	13.919	.079	.078

before treatment the classical picture of active rickets was found, namely a high faecal output of CaO and P_2O_5. During treatment a very high retention of CaO and P_2O_5 was brought about by a marked diminution in the faecal output of these substances. The most marked increase in retention was obtained with direct irradiation, the retention of lime being increased during this treatment roughly 6 times. With the use of vigantol and cod-liver oil the retention of CaO was increased approximately 4 times, and with radiostol $2\frac{1}{2}$ times.

Metabolism studies were also obtained in the 2 older children belonging to Group I (Table XXIX). Owing, however, to the slight differences in the mode of excretion and retention at this later age these figures cannot be compared directly with the figures for the metabolic studies in the younger patients. In both patients before treatment there was a high faecal output of CaO and P_2O_5 causing in Case 4, a slightly negative balance of CaO and a very low positive retention of P_2O_5 and in Case 5, M.O'N, a low positive balance of CaO and P_2O_5. During treatment with irradiation the retentions of CaO and P_2O_5 in both cases were markedly increased owing to a great diminution in the faecal output of these substances.

TABLE XXX.

Analysis of faeces before and during treatment of infantile rickets.

	Case 3. (Irradiation)		Case 7. (Radiostol)		Case 12. (vigantol).		Case I4 (Cod Liver Oil).	
	1st Period.	2nd Per.	Ist.Per	2nd.Per	Ist.Per	2nd.Per	1st.per	2nd.Per.
Faecal Wt. (gm.)	66.14	32.13	125.65	71.25	80.4	82.15	69.17	48.0
% Ash	49.0	18.8	24.0	17,5	33.28	15.15	36	21.8
Total CaO (gm.)	14.286	2.121	9.047	5.771	10.693	4.600	9.753	4.272
Total P_2O_5 (gm.)	13.823	1.606	8.293	2.137	10.613	1.807	10.721	3.126
% CaO	21.6	6.6	7.2	8.06	13.3	5.6	14.1	8.9
% P_2O_5	20.9	5.0	6.6	3.0	13.2	2.2	15.5	6.7
Total fat (gm.)	17.217	14.139			34.588	35.357	15.978	18.408
Neutral fat (gm)	2.097	2.406			5.974	4.116	3.711	2.592
Free Fatty acids. (gm)	7.857	4.510			19.754	9.324	5.883	9.72
Combined fatty acids. (gm)	7.263	7.223			8.860	21.918	6.384	6.096
% T.F.	26.03	44.01			43.02	43.04	23.10	38.35
% N.F.	3.17	7.49			7.43	5.01	5.365	5.4
% F.F.A.	11.88	14.04			24.57	11.35	8.505	20.25
% C.F.A.	10.98	22.48			11.02	26.68	9.23	12.70

TABLE XXXI.

Analysis of faeces before and during treatment of late rickets.

	Case 4 (Irradiation)		Case 5 (Irradiation)	
	Ist.Per	2nd.Per	Ist. per	2nd.per.
Faecal wt. gm.	110.15	32.20	76.76	42.06
% Ash	31.8	21.4	44.54	27.2
Total CaO. gm.	17.293	2.673	14.431	4.753
Total P_2O_5- gm.	12.006	1.803	13.970	4.332
% CaO	15.7	8.3	18.8	11.3
% P_2O_5-	10.9	5.6	18.2	10.3
Total Fat gm	18.758	10.052	18.775	11.971
Neutral Fat (gm)	3.205	2.088	2.583	2.402
Free Fatty Acids. (gm)	4.164	2.043	6.321	1.817
Combined fatty acids (gm)	11.389	5.921	9.871	7.752
% T.F.	17.03	31.22	24.46	28.46
% N.F.	2.91	6.485	3.365	5.71
% F.F.A.	3.78	6.345	8.235	4.32
% C.F.A.	10.34	18.39	12.86	18.43

The results of the analysis of the faeces with regard to the percentage composition and the total content of CaO, P_2O_5 and fat are shown in Tables XXX and XXXI. It will be noted that not only is there a marked reduction in the faecal weight during healing but that also a marked decrease occurs in the percentage of ash and in the percentage of CaO and P_2O_5. This is accompanied by an increase in the percentage of total fat and also in the percentage of combined fatty acids. The increase in the percentage of combined fatty acids associated with the relatively greater decrease in percentage of P_2O_5 than percentage of CaO is further evidence of the now well known fact that during the healing phase of rickets there is more faecal CaO in the form of soaps and less in the form of Ca phosphate.

In assessing the value of the different methods of treatment practical considerations make it necessary to take into account other features than the small differences in the rapidity of healing. Although direct irradiation produces immediate and rapid healing it is not from a practical standpoint the method of choice. The disadvantages of this method include the initial cost of the apparatus, the necessity for constant skilled supervision to avoid damage from excessive exposure, and the frequent regular

attendance of the patient at the clinic. The simple oral administration of a preparation rich in the anti-rachitic agent would seem at once more convenient for doctor and patient. In choosing between cod-liver oil and preparations such as radiostol and vigantol the question of cost is important particularly when one is dealing with the large numbers of patients which require to be treated in hospital practice and Child Welfare Clinics. From this point of view cod-liver oil is undoubtedly the method of selection. An objection which has frequently been raised against the use of cod-liver oil is the difficulty met with in inducing children to take it. Our experience, however, has been that most children do not object to it and in the few who do, a little persistence usually overcomes their initial dislike. A more important objection is the variable content of the anti-rachitic vitamin in different brands of the oil, but the use of a brand of known anti-rachitic value readily overcomes this disadvantage.

Summary.

Effective healing was brought about by each of the 4 methods of treatment. In the mineral metabolism of every case there was produced to a marked degree the changes

typical of the healing phase of the disease. The highest retentions of CaO and P_2O_5 occurred during treatment with direct irradiation but equally rapid healing as judged radiologically and from estimations of the serum Ca and P was produced by the use of cod-liver oil and vigantol while a somewhat slower improvement, as estimated by all standards, occurred during the administration of radiostol.

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METHODS:

Calcium Content of Serum: Kramer and Tisdall.

Inorganic Phosphorus Content of Serum: Tisdall.

Total CO_2 of Blood: Haldane.

Urinary Chlorine: Volhard.

Titratable Acidity of Urine: phenolphthalein used as indicator.

CaO in milk and faeces was precipitated as oxalate, washed and titrated with $^{N}/_{10}$ $KMnO_4$; in urine it was weighed after precipitation and reduction.

P_2O_5 in milk, urine and faeces was precipitated as magnesium phosphate, reduced, and weighed.

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REFERENCES.

1. Pritchard, E.: Brit.Med.Journ. 1923 1 887.

2. Hodgson, A.: Lancet 1921, 2 945.

3. Freudenberg, E. and György, P.: Munch.med.wchshr. 1922, 12 422.

4. Burgess, N. and Osman, A.A.: Lancet 1924 1 281.

5. György, P., Avitaminosen (Rachitis), Stepp & György, J.Springer, Berlin 1927.

6. Bosanyi, A.: Jahrb.f.Kinderh. 1927 117 240.

7. Schabad; Arch.f.Kinderh. 1910 53 380.
   ibid. 1910 54 83.

8. Zucker, T.F., Johnson, W.C. and Barnett, M.: Proc.Soc. Exp.Biol.& Med., 1926, 20 20.

9. Hess, A.F., Weinstock, M., Rivkin, H., and Gross: Proc. Soc.Exp.Biol. & Med., 1929, 27 140.

10. Telfer, S.V.; Quart.Journ.Med., 1922-23, 16 45 and 63.
    ibid. 1923-24, 17 245.
    ibid. 1926 , 20, 7.

11. György, P.: Ergeb.der inner Med und Kind. 1929 36 752.

12. Findlay, L., Paton, D.N., and Shapre, J.G.: Quart.Journ. Med. 1921, 14 362.

13. Howland, J.: Medicine 1923 11 349.

14. Zucker, T.F. and Gutman, M.: Proc.Soc.Exp.Biol.and Med. 1926, 20 372.

15. Bergeim, O.: Journ.Biol.Chem., 1926, 70 51.

16. Findlay, L.: Journ.Amer.Med.Ass., 1924, 83 1473.

17. Murdoch, G.: Arch.Dis.Child., 1927, 2 285.

18. Hjort, A.M.: Journ.Biol.Chem., 1925, 45 783.

19. Denis, W., and Minot A.S.: Journ.Biol.Chem., 1920 41 357.

20. Jansen, W.H.: Klin.Wchschr., 1924, 3 715.

21. Kahn., B.S., and Roe, J.H.: Journ.Amer.Med.Ass., 1926 86 1761.

22. Bauer, W. and Ropes, M.W.: Journ.Amer.Med.Ass., 1926 87 1902.

23. Klercker, K., and Odin, M.: Acta Paed., 1925, 5 79.

24. Warkany, J.: Zeit f.Kinderh. 1928 46 1.

25. MacClendon, J.F., Myers, Culligan and Geydesen: Journ. Biol.Chem. 1919, 38 535.

26. MacClendon, J.F., Bissell, F.S., Lowe, E.R., and Meyer P.F.: Journ.Amer.Med.Ass., 1920, 75 1638.

27. Arnold, L.: Klin.Wchnschr., 1927 I 607.

28. Wills, L., Sanderson, P., and Paterson, D.: Arch.Dis. Child, 1926 1 245.

29. Schloss, E.: Ergeb.d.inn.Med.u.Kinderheilk., 1917, 15 55.

30. Redman, T.: Biochem.Journ. 1929 23 256.

31. Zucker, T.F. and Matzer M.J.: Proc.Soc.Exp.Biol. & Med., 1923 21 186.

32. Jephcott, H. and Bacharach, A.L.: Biochem.Journ. 1926, 20 1350

33. Yoder, L.: Journ.Biol.Chem., 1927 74 321.

34. Redman T., Willimot, S.G., and Wokes, F.: Biochem.Journ., 1927 21 589.

35. Grayzel, D.M., and Millar, E.G.: Journ.Bio.Chem., 1928, 76 423.

36. Tisdall, F.F., and Price, H.W.: Bull.Johns.Hop.Hosp., 1927 41 432.

37. Haldane, J.B.S.: Journ.Physiol., 1921, 55 265.

38. Steenbock, H.: Nelson, M.V. and Hart E.B.: Journ.Biol. Chem., Baltimore, 1914 19 399.

39. Sawyer, M., Baumann, L., and Stevens, F.: ibid. 1918, 33 103.

40. Bogert, L.J., and Kirkpatrick, E.E.: ibid. 1922 54 375.

41. Flood, R.S.: Amer.Journ.Dis.Child., 1926, 32 550.

42. Koehler, A.E.: Journ.Biol.Chem., 1927, 72 99.

43. Keith, N.M., and Whelan, M.: Journ.Clin.Invest., 1926-7, 3 149.

44. Stewart, C.P. and Haldane, J.B.S.: Biochem.Journ., 1924, 18 856.

45. Haldane, J.B.S., Wigglesworth, V.B., and Woodrow, C.E.: Proc.Roy.Soc.Biol., 1924 96 1.

46. Gamble, J.L., Ross, S.G., and Tisdall, F.: Amer.Journ. Dis.Child., 1923, 25 455.

47. Goto, K.: Journ.Biol.Chem., 1918, 36 355.

48. Grosser, P.: Ztschr.f.Kinderh., 1920 25 141.

49. Salvesen, H.A.: Journ.Biol.Chem., 1923 56 443.

50. Percival, G.H. and Stewart, C.P.: Biochem.Journ., 1927, 21 301.

51. Bauer, W., Albright, F., and Aub, J.C.: Journ.Clin. Invest., 1929, 7 75.

52. Givens, M.H., and Mendel, L.B.: Journ.Biol.Chem., 1917, 31 421.

53. Nelson, M.V.; Amer.Journ.Dis.Child., 1928, 36 716.

54. Shohl, A.T., and Sato, A.: Journ.Biol.Chem., 1923 58 235.

55. Benedict, S.R. and Nash, T.P.: Journ.Biol.Chem., 1926, 69 381.

56. Morris, N. and MacRae, O.: Arch.Dis.Child., 1930 5 207.

57. Gassmann, T.: Ztschr.f.physiol.Chem., 1910, 70 161.
Ztschr.f.Physiol. 1913, 83 403.
ibid. 1918, 90 250.

58. Meyer, L.F.: Zahrh.f.Kinderh. 1910 71 1.

59. Freudenberg, E. and Györgyy, P.: Zahrh.f.Kinderh. 1921 96 5.
Klin.Wchschr. 1922 1 410.

60. Drucker, P.: Journ.Biol.Chem. 1926 68 57.
Acta Paed., 1927 6 1.

61. Iverson, P., and Lenstrup, E.: Forhand.ved.Forste.Nordiske, Kongres.f.Paediat., 1922. (quoted by Howland & Kramer (62)).

62. Howland, J., and Kramer, B.: Amer.Journ.Dis.Child., Chicago, 1921, XXII, 105.

63. Hess, A.F., and Unger, L.J.: Amer.Journ.Dis.Child,, Chicago, 1922, XXIV, 327.

64. Hess, J.H., Calvin, J.K., Wang, C.C., and Felcher, A.: Amer.Journ.Dis.Child., Chicago, 1923, XXVI, 271.

65. Huntly, W.: Ajmere Rajputana Press 1889. Quoted by Findlay, L., Brit.Med.J., London, 1922, ii, 846.

66. Huldschinsky, K.: Deutsche Med.Woch., Leipzig, 1919, xlv.712.
Zeit.f.Orth.Chir., Stuttgart, 1919-20 xxxix 426

67. Chick, H., et alia: Medical Research Council Special Report Series, London, 1923, No.77, 74.

68. Braine, J.Carter, and Osman, A.A.: Guy's Hosp.Rep., London, 1925, lxxv, 491.

69. Kramer, B., Casparis, H., and Howland,J.: Amer.J.Dis. Child., Chicago, 1922. xxiv, 20.

70. Meyer, L.F.: Internat.Clin., Philadelphia, 1921, iv, 176.

71. Orr, W.J., Holt, L.E., Wilkins, L., Boone, F.H.: Amer. Journ.Dis.Child., Chicago, 1923, xxvi, 362.

72. Karelitz, S.: Proc.Soc.Exp.Biol. and Med., New York, 1928, xxv, 576.
Amer.Journ.Dis.Child., Chicago, 1928, xxxvi, 1108.

73. Gyorgy, P.: Strahlentherapie, Berlin, 1928, xxviii, 359.

74. Vollmer, H.: Monat.f.Kind., Leipzig, 1928, xxxviii, 70.

75. Aidin, R.: Lancet, London, 1928, i, 229.

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