THE VALUE OF DIFFERENT THERAPEUTIC AGENTS IN THE TREATMENT OF RICKETS

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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 the present work is to demonstrate the relative value of some of these different methods by a comparative study of their influence on the radiological picture, the calcium and phosphorus contents of the blood, and the retentions of calcium and phosphorus.

Although the absence of sunlight as a cause of rickets was suggested by Huntly¹ as long ago as 1889 it was not until 1919 that, in consequence of the work of Huldshinsky² definite evidence was brought forward. This author was successful in effecting cure by exposure of the body to ultra-violet rays emanating from a mercury-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 two to five weeks. Chick³ in Vienna noted healing in from two to four weeks after commencement of irradiation and Carter Braine and Osman⁴ report cases in which healing appeared after two to five weeks of ultra-violet ray therapy. In a series of five cases Kramer, Casparis and Howland⁵ reported the effect of irradiation on the X-ray picture and the blood serum findings. They noted that healing became evident within four weeks from commencement of treatment and that the inorganic phosphorus content of the blood rose from 3 to 6 mgrm. per 100 c.cm. of serum in 6 to 11 weeks.

Fewer cases have been reported in which the retention of lime has been studied. In 1921 Meyer⁶ 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 two cases he found a considerable increase in the retention of lime during ultra-violet light treatment. Orr, Holt, Wilkins and Boone⁷ have also reported an increase in the retentions of CaO and P₂O₅ 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 P₂O₅. Karelitz⁸, giving vigantol in doses

equivalent to 3.3 mgrm. of irradiated ergosterol daily, found healing in the radiographic picture as early as 7 days. The average time of the first appearance of healing however was 21 days from commencement of treatment, and the inorganic phosphorus content of the serum rose to normal in 14 to 21 days. Gyorgy⁹, Vollmer¹⁰ and other German workers also using vigantol have reported similar results. In a series of 5 cases treated with radiostol Aidin¹¹ found the earliest radiological evidence of healing in from 3 to 8 weeks.

Present investigations.—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 three weeks before the commencement of treatment, and with two 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 .

METHODS. The method used for the determination of the calcium content of the serum was that of Kramer and Tisdall¹², and Tisdall's¹³ method was used for the determination of the inorganic phosphorus content of the serum.

In all cases in which it was possible a metabolic study was made before treatment and during the second week of treatment. Each metabolic study extended over a period of seven days, the diet being constant for at least three days prior to the actual metabolic investigation. The usual gravimetric methods were used for the determination of CaO in urine and of P_2O_5 in faeces, urine, and milk. Lime in the faeces and milk was precipitated as oxalate and titrated with deci-normal permanganate.

The cases are divided into four groups according to the method of treatment employed.

Group 1 consists of five cases who received direct irradiation of the skin. Of these, three were examples of ordinary infantile rickets, and the other two were older children, a boy aged $9\frac{1}{2}$ years and a girl aged 12 years. The boy (Case 4) 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 genu valgum. In the case of the girl it was noted that 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 mercury-vapour quartz-lamp at a distance of 4 ft. The exposures were increased daily according to the tolerance of the skin.

Group 2 includes four examples of infantile rickets treated with radiostol. Three of the children received 4 min. of a solution of radiostol in oil three times daily; and one, who was an out-patient (Case 9) was given two radiostol pellets daily.

In Group 3 are three cases (one of which, Case 10, was an out-patient) treated with two pellets of vigantol daily (1 pellet=4 mgrm. irradiated ergosterol).

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Group 4 includes two cases treated with one drachm of cod-liver oil three times daily.

The results are summarized in Table 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

TABLE 1.

EFFECT OF DIFFERENT FORMS OF TREATMENT ON RADIOGRAMS, SEROLOGICAL FINDINGS AND MINERAL RETENTION.

Case No.	Age in years	Treatment	Radiograms.		Blood chemistry.				Daily retention per krgm.			
			First appearance of healing	Subsequent healing	Before treatment.		End of 2nd week of treatment.		Before treatment.		End of 2nd week of treatment.	
					Serum Ca mgrm. %	Serum P mgrm. %	Serum Ca mgrm. %	Serum P mgrm. %	CaO grm.	P ₂ O ₅ grm.	CaO grm.	P ₂ O ₅ grm.
1	1 $\frac{8}{12}$	Irradiation	3 weeks	rapid	8.13	2.5	10.47	4.3	—	—	—	—
2	2 $\frac{5}{12}$	"	12 days	"	9.56	2.8	—	5.8	—	—	—	—
3	2 $\frac{7}{12}$	"	2 weeks	"	7.29	4.3	10.09	4.3	+0.39	+0.45	+0.255	+0.220
4	9	"	2 weeks	"	—	4.1	—	6.4	—0.03	+0.04	+0.10	+0.08
5	12	"	4 weeks	slow	11.2	3.0	11.08	5.2	+0.03	+0.02	+0.08	+0.08
6	1 $\frac{9}{12}$	Radiostol	4 $\frac{1}{2}$ weeks	slow	—	3.4	—	4.0	—	—	—	—
7	1 $\frac{10}{12}$	"	2 weeks	rapid	8.46	4.0	9.9	5.1	+0.42	+0.43	+0.104	+0.080
8	3 $\frac{1}{2}$	"	3 weeks	slow	10.04	3.0	—	4.4	—	—	—	—
9	3 $\frac{1}{2}$	"	5 $\frac{1}{2}$ weeks	slow	8.6	3.1	9.2	3.7 (7 $\frac{1}{2}$ wks.)	—	—	—	—
10	2 $\frac{1}{2}$	Vigantol	2 weeks	rapid	9.2	2.0	9.4	4.1	—	—	—	—
11	1 $\frac{1}{2}$	"	1 week	rapid	5.1	7.1	8.1	4.4	—	—	—	—
12	1 $\frac{1}{2}$	"	1 week	slow	4.0	4.8	10.2	9.2 (3 wks.)	+0.27	+0.37	+0.124	+0.097
13	2	Cod-liver oil	17 days	rapid	10.04	3.0	—	4.0	—	—	—	—
14	2	"	18 days	rapid	8.5	2.1	8.84	3.33	+0.39	+0.48	+0.153	+0.156

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. 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 (see Table 1).

Changes in serum calcium and phosphorus.—GROUP 1. The behaviour of the serum calcium and phosphorus in the group of cases treated with ultra-violet light is shown in Charts I and II. Two of these cases (No. 1 and 3) were complicated by latent tetany, and in both the serum calcium rapidly rose to normal after 1 to 3 weeks of treatment. In four of the cases the initial level of the serum phosphorus was low, varying from 2.1 to 3.9 mgrm., and rose to a maximum of between 6.5 and 7 mgrm. in 2 $\frac{1}{2}$ to 6 weeks. Chart II illustrates the continued improvement in Case 3 after the cessation of treatment.

CHART I.

TREATMENT WITH ULTRA-VIOLET LIGHT.

CHART II.

TREATMENT WITH ULTRA-VIOLET LIGHT.

Case 3. (rickets and latent tetany) showing continued improvement after cessation of treatment.

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GROUP 2. In the cases treated with radiostol the blood changes were not so marked (Chart III). In Case 6, which had an initial normal serum calcium of 9.49 mgrm. per 100 c.cm. and a serum phosphorus of 3.4 mgrm., the rise in the serum phosphorus to a maximum of 5.8 mgrm. occurred in 6½ weeks. In Case 8, which also had a normal serum calcium, the phosphorus had not risen above 4.7 mgrm. at the end of 6 weeks of treatment. Administration of radiostol was then omitted and cod-liver oil in one-drachm doses given three times daily. The serum phosphorus rose rapidly reaching a height of 8 mgrm. in two weeks, thereafter showing a gradual fall. In Case 9, which was treated as an out-patient, it took 7½ weeks for the serum phosphorus to rise from 3.1 to 3.7 mgrm., and the serum calcium to rise from 8.6 to 9.2 mgrm. (Table 1).

CHART III.
TREATMENT WITH RADIOSTOL.

In Case 7, which had had an initial serum calcium of 8.5 mgrm. and serum phosphorus of 4.0 mgrm. the values of both rose rapidly to 11.1 and 6.1 mgrm. respectively after treatment for three weeks.

GROUP 3. In the two in-patients (Cases 11 and 12) who were treated with vigantol, Chvostek's sign was present and both had laryngismus. The serum calcium was very low, being 5.1 mgrm. in Case 11, and 4.0 mgrm. in Case 12. After three weeks treatment the value for the serum calcium rose in the former to 9.1, and in the latter to 10.2 mgrm. (Chart IV). In Case 10, which was treated as an out-patient, the initial serum calcium was normal. The serum phosphorus which was 2.0 before treatment rose to 4.1 mgrm. in 2 weeks (Table 1).

GROUP 4. Of the two children treated with cod-liver oil one (Case 14) had latent tetany, the serum calcium being 8.5 mgrm. During the first four

CHART IV.
TREATMENT WITH VIGANTOL.

weeks of treatment this figure varied between 8.8 and 9.2 mgm., and then rose to 10.8 at the end of $7\frac{1}{2}$ weeks while the value for the serum phosphorus showed a gradual increase from 2.1 to 5.4 mgm. In the other patient (Case 13) whose serum calcium was normal, the serum phosphorus showed a more rapid increase, reaching a maximum of 7 mgm. in $6\frac{1}{2}$ weeks (Chart V).

CHART V.
TREATMENT WITH COD-LIVER OIL.

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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 phosphorus was somewhat less marked.

Metabolism studies.—A study of the calcium and phosphorus metabolism was obtained in one case of infantile rickets from each of the four groups. The results are shown in Table 2. In all the cases 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

TABLE 2.
METABOLISM OF CaO AND P_2O_5 IN FOUR CASES OF INFANTILE RICKETS
BEFORE AND DURING SECOND WEEK OF TREATMENT

Case No.	Age in years	Period	Total intake		Total output		Faecal output		Urinary output		Ratio $\frac{Ur. P_2O_5}{Faec. P_2O_5}$	Total retention		Daily retention per kgm.	
			CaO gm.	P_2O_5 gm.	CaO gm.	P_2O_5 gm.	CaO gm.	P_2O_5 gm.	CaO gm.	P_2O_5 gm.		CaO gm.	P_2O_5 gm.	CaO gm.	P_2O_5 gm.
3	$2\frac{7}{12}$	Before treatment	16.632	21.672	14.336	18.993	14.286	13.823	.050	5.17	$\frac{1}{2.7}$	2.296	2.679	.039	.045
		During irradiation ..	16.632	21.672	2.204	9.201	2.121	1.606	.083	7.595	$\frac{4.7}{1}$	14.428	12.471	.255	.220
7	$1\frac{6}{12}$	Before treatment ..	11.157	15.592	9.082	13.473	9.047	8.293	.035	5.18	$\frac{1}{1.6}$	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	$\frac{4.4}{1}$	5.231	4.035	.104	.080
12	$1\frac{6}{12}$	Before treatment ..	12.60	17.64	10.869	15.331	10.693	10.613	.176	4.718	$\frac{1}{2.2}$	1.731	2.309	.027	.037
		During administration of Vigantol ..	12.60	17.64	4.82	11.551	4.60	1.807	.220	9.744	$\frac{5.3}{1}$	7.780	6.091	.124	.097
14	$2\frac{2}{12}$	Before treatment ..	11.76	16.17	9.848	13.849	9.753	10.721	.095	3.128	$\frac{1}{3.4}$	1.912	2.321	.039	.048
		During administration of Cod-Liver oil	11.76	16.17	4.356	8.735	4.272	3.126	.084	5.609	$\frac{1.8}{1}$	7.404	7.435	.153	.156

about by a marked diminution in the faecal output of these substances. The greatest increase in retention was obtained with direct irradiation, the retention of lime being increased during this treatment roughly six times. With the use of vigantol and cod-liver oil the retention of CaO was increased approximately four times, and with radiostol $2\frac{1}{2}$ times. It is interesting to note that the urinary output of P_2O_5 was increased during the healing phase in every case, and the excretion of CaO by the kidneys was increased during healing in every instance except Case 14, in which practically no change was noted.

Metabolism studies were also obtained in the two older children belonging to Group 1 (Table 3). 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

TABLE 3.

METABOLISM OF CaO AND P₂O₅ IN TWO OLDER CHILDREN BEFORE AND DURING SECOND WEEK OF TREATMENT.

Case No.	Age in years	Period	Total intake		Total output		Faecal output		Urinary output		Ratio $\frac{\text{Ur. P}}{\text{Faec. P}}$	Total retention		Daily retention per kgrm.	
			CaO grm.	P ₂ O ₅ grm.	CaO grm.	P ₂ O ₅ grm.	CaO grm.	P ₂ O ₅ grm.	CaO grm.	P ₂ O ₅ grm.		CaO grm.	P ₂ O ₅ grm.	CaO grm.	P ₂ O ₅ grm.
4	9	Before treatment	16.80	23.10	17.362	22.507	17.293	12.006	.069	10.501	$\frac{1}{1.14}$	—0.55	+0.593	—003	+002
		During irradiation	16.80	23.10	2.776	11.798	2.673	1.803	.103	9.995	$\frac{5.5}{1}$	14.024	11.302	+0.099	+0.080
5	12½	Before treatment	20.16	27.72	14.719	23.573	14.431	13.97	.288	9.603	$\frac{1}{1.4}$	5.441	4.15	+0.029	+0.022
		During irradiation	20.16	27.72	6.073	13.801	4.753	4.332	1.32	9.469	$\frac{2.2}{1}$	14.087	13.919	+0.079	+0.078

TABLE 4.

ANALYSES OF FÆCES BEFORE AND DURING TREATMENT OF INFANTILE RICKETS.

		Case 3. (Irradiation)		Case 7. (Radiostol)		Case 12. (Vigantol)		Case 14. (Cod-liver oil)	
		1st Per.	2nd Per.	1st Per.	2nd Per.	1st Per.	2nd Per.	1st Per.	2nd Per.
Faecal wt. (grm.)	..	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	36.0	21.8
Total CaO (grm.)	..	14.286	2.121	9.047	5.771	10.693	4.600	9.753	4.272
Total P ₂ O ₅ (grm.)	..	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 ₂ O ₅		20.9	5.0	6.6	3.0	13.2	2.2	15.5	6.7
Total fat (grm.)		17.217	14.139			34.588	35.357	15.978	18.408
Neutral fat (grm.)	..	2.097	2.406			5.974	4.116	3.711	2.592
Free fatty ac. (grm.)	..	7.857	4.510			19.754	9.324	5.883	9.72
Comb. fatty ac. (grm.)	...	7.263	7.223			8.860	21.918	6.384	6.096
% total fat		26.03	44.01			43.02	43.04	23.10	38.35
% neutral fat		3.17	7.49			7.43	5.01	5.365	5.4
% free fatty ac.	..	11.88	14.04			24.57	11.35	8.505	20.25
% comb. fatty ac.		10.98	22.48			11.02	26.68	9.23	12.70

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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, 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. Unlike the younger children no increase occurred in the excretion of P_2O_5 by the kidneys during healing, the amount excreted during both periods being within normal limits.

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 4 and 5. It will be seen that not only is there a marked reduction in the

TABLE 5.
ANALYSES OF FECES BEFORE AND DURING TREATMENT OF LATE RICKETS.

					Case 4. (Irradiation)		Case 5. (Irradiation)	
					1st Per.	2nd Per.	1st Per.	2nd Per.
Faecal weight (grm.)	..	..	..	..	110.15	32.20	76.76	42.06
% Ash	..	..	..	..	31.8	21.4	44.54	27.2
Total CaO (grm.)	..	..	..	..	17.293	2.673	14.431	4.753
Total P_2O_5 (grm.)	..	..	..	..	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	10.2
Total fat (grm.)	..	..	..	..	18.758	10.052	18.775	11.971
Neutral fat (grm.)	..	..	..	..	3.205	2.088	2.583	2.402
Free fatty acid (grm.)	..	..	..	..	4.164	2.043	6.321	1.817
Comb. fatty acid (grm.)	..	..	..	..	11.389	5.921	9.871	7.752
% total fat	..	..	..	..	17.03	31.22	24.46	28.46
% neutral fat	..	..	..	..	2.91	6.485	3.365	5.71
% free fatty ac.	..	..	..	..	3.78	6.345	8.235	4.32
% comb. fatty ac.	..	..	..	..	10.34	18.39	12.86	18.43

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 lime in the form of soaps and less in the form of calcium phosphate.

Discussion.

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 pro-

duces 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 in view of the large numbers of children requiring treatment in hospital practice and welfare clinics. From this aspect cod-liver oil is undoubtedly the method of selection. An objection which has frequently been raised to 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 any 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 four 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 calcium and phosphorus was produced by the use of cod-liver oil and vigantol. A somewhat slower improvement, as estimated by all standards, occurred during the administration of radiostol.

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