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AN

Experimental Investigation

ON

RICKETS

Two Lectures Delivered at the Royal College of Surgeons of England

BY

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RICKETS.

LECTURE I.

HAVING described in the first two lectures of this course the experimental results obtained in a Research on Alcohol for the Central Control Board (Liquor Traffic), I propose in the next lectures to deal with another social evil—rickets—and to give an account of an experimental investigation made for the Medical Research Committee with the object of finding the essential cause of this disease.

THE SERIOUS RESULTS OF RICKETS.

It is but little realised how great and how widespread is the part played by rickets in civilised communities. If the matter ended with bony deformities obvious to the eye it would be bad enough, but investigations have demonstrated that such deformities only represent a small part of the cases affected. Schmorl's histological investigations on children dying before the age of 4 years showed that 90 per cent. had had rickets. Again, Lawson Dick's examination of the children in London County Council schools, and more particularly the examination of their teeth, led him to state that 80 per cent. of such children had had rickets. The relation between rickets and defective teeth has been placed on an experimental basis recently by the work of my wife,[1] and there can be little doubt that any remedy which would exclude the one would almost certainly improve and might eradicate the other. The rachitic child, in fact, carries the stigma of the disease throughout life in the form of defective teeth.

Nor is this the most serious part of the evil, for the reduced resistance to other diseases of the rachitic child

[1] THE LANCET, 1918, ii., 767.

and animal is so marked that the causative factor of rickets may be the secret of immunity and non-immunity to many of the children's diseases which result in the high death-rate associated with urban conditions. It is a striking fact to remember that in the West of Ireland, where the death-rate is only 30 per 1000, rickets is an unknown disease, whereas in poor urban districts of this country where rickets is rife the death-rate in children varies from 100 to 300 per 1000. It is at least suggestive that there may be some relation between rickets and the enormous death-rate of towns, even although the disease in itself does not kill.

The experimental work I wish to describe in these lectures has shown that the rachitic condition need not be at all advanced before the animal's whole behaviour is transformed. It becomes lethargic and is far more liable to be affected by distemper and broncho-pneumonia and is very susceptible to mange. The low resistance of animals which develops as the result of conditions which ultimately lead, under favourable circumstances, to rickets is impressive.

So many of the conclusions regarding the ætiology of rickets have been based on a small number of experiments that it may not be out of place to record that this investigation, undertaken for the Medical Research Committee, has already involved the use of 200 puppies and is still incomplete.

On referring to the literature at the beginning of the research it was soon obvious that the number of hypotheses put forward to explain the ætiology of rickets was legion, while discussion on the subject with those having clinical knowledge only emphasised the completely speculative nature of the ideas held by those whose business it is to deal with the disease.

A considerable number of experiments were first made in an attempt to see whether the ætiology of rickets was to be sought along non-dietetic lines and it was only after failure that the dietetic solution was resorted to. This type of work has continued and has clearly shown that, however important other factors may be, and that there are other factors is not denied, the dietetic problem is the primary key to the situation. In the next lecture some of the more commonly held hypotheses of rickets will be mentioned and discussed in relation to the results obtained in this work.

Experimental Methods.

Although it is well recognised that different breeds of dogs vary considerably in their susceptibility to rickets, no special type has been used in this work. In some ways this may be disadvantageous ; but, on the other hand, to be driven to associate rickets with a particular breed is in itself unsatisfactory and obviously leads the investigator into a blind alley if the ultimate object is to extend the results to children.

The experimental methods used to detect rickets have depended on (1) X ray examination of the bones ; (2) calcium estimation of the bones after death ; (3) histological preparations of the bones.

The calcium estimation of the bones has been made by Cahen and Hurtley's modification of the oxalate method. In comparative estimations it is useful ; but, since it is well recognised that the calcium content of bones varies considerably and independently of the rachitic condition, this method can never be used alone and must always be controlled by histological examination. [In the lecture further details of the methods were described and X ray photographs and histological specimens were demonstrated by means of the epidiascope].

In these lectures I propose to illustrate the normality and degree of rickets obtained by means of the calcium oxide content of the bones. Histological preparations can be seen if desired and also the X ray photographs of many of the dogs. In all cases histological preparations of the bones were made and corresponded, in comparative experiments, with the CaO results given.

[A series of puppies with and without rickets was then shown]. In the puppies exhibited it will be observed that the differences between normal and rachitic puppies are similar to the differences between normal and rachitic children. Like the rachitic child, the puppy shows abnormally large swellings at the epiphyseal ends of the bones ; it has a marked rickety rosary, its tendons and ligaments are loose, the bones tend to bend, and thereby help to exaggerate the leg deformity. The amount of deformity often depends on the weight of the animal. Again, the rachitic puppy is lethargic and does not jump about ; its power to run, apart from the leg deformity and before this develops, is comparatively limited ; there is, in fact, a general loss of tone of the musculature. Similarly, just as the rachitic baby is a good baby and does not cry much, so also the dog in this condition seldom barks or makes the superfluous efforts practised by the normal healthy puppy.

The puppies were started on their diets after leaving the mother, the ages varying between 5 and 8 weeks, the latter being the more usual. They were kept for varying periods according to the type of experiments. In the earlier periods they were usually killed after five to six months, but as the work progressed and the diets became more rachitic this time was considerably shortened.

Determination of Rachitic Diet.

Having determined to see what part diet played as a causative factor in rickets, it was necessary to get a standard diet which would always produce this condition in the experi-

mental animals. The first diet used consisted of whole milk (175 c.cm. per diem) and porridge made up of equal parts oatmeal and rice, together with 1–2 g. NaCl. The oatmeal and rice was later replaced by bread and found to be as effective and easier to use. This second diet was afterwards modified as the experimental results were obtained. The following four diets (Table I.) have therefore been used

TABLE I.—*Rachitic Diets.*

Diet I.	Diet II.	Diet III.	Diet IV.
Whole milk, 175 c.cm.	Whole milk, 175 c.cm.	Separated milk, 175 c.cm.	Separated milk, 250–350 c.cm.
Oatmeal, rice.	Bread ad lib.	Bread (70 per cent. wheaten) ad lib.	Bread (70 per cent. wheaten) ad lib.
1–2 g. NaCl.		Linseed oil, 10 c.cm.	Linseed oil, 5–15 c.cm.
		Yeast, 10 g.	Yeast, 5–10 g.
		NaCl, 1–2 g.	Orange juice, 3 c.cm.
			NaCl, 1–2 g.

during the course of the work, each one of which is a rachitic diet under laboratory conditions.

The modifications of the diets were carried out in order to : (1) ensure a more rapid development of rickets ; (2) to be compatible with better health and better rate of growth. As will be seen later, the better the animal grows on a rachitic diet the more easily is rickets produced or rather the more difficult it is to stop. In the close examination of foodstuffs from this point of view, this is eminently desirable. It is undesirable in such work to have animals in a semi-starved condition involving a high mortality due to bronchopneumonia and marasmus. Puppies, like all young animals, tend to develop these diseases unless the diet is well chosen.

RESULTS OF ADDITION OF VARIOUS SUBSTANCES TO RACHITIC DIET.

Having obtained diets which normally produce rickets, various substances were added and the effect on the development of the disease noted. In the following tables the quantity of calcium estimated as CaO present in the shaft of the femurs of the animals fed on these diets is given. In the last column the histological findings of the bones examined are added.

TABLE II.—*Diet I. plus more Whole Milk.*

No. of experiment.	Diet.	Duration. Months.	Initial weight.	Final weight.	Gain.	CaO in femur shaft. Dry.	CaO in femur shaft. Fresh	Histology results.
			g.	g.	g.	%	%	
43	Diet I.	4	905	2187	1282	23·5	—	Rickets.
52	,,	8	1745	5200	3455	23 5	—	,,
53	,,	7½	1765	4245	2480	22·5	—	,,
56	+ 325 c.cm. milk.	5	1810	5280	3470	31·8	—	Normal.
57	+ 325 ,, ,,	5	1330	4980	3650	29 2	—	,,

TABLE III.—*Diet II. plus Meat and Meat Extracts.*

73	Diet II.	4	3950	6110	2160	20 7	—	Rickets.
96	+ dog biscuit.	5½	1905	4200	2295	22·1	9·38	,,
97	,,	5½	1375	3295	1920	16·03	5·90	,,
68	+ Wat. ext. of meat.	4	4000	6540	2540	32 8	—	Normal.
69	+ Meat protein.	5	4840	7630	2790	21·7	—	Rickets.
70	+ 80% alc. ext. of meat.	5	4577	6695	2118	30·2	—	Normal.
93	+ 10 g. meat.	5½	1220	7450	6230	29·53	15·43	,,

TABLE IV.—*Diet II. plus Yeast and Malt Extract.*

96	Diet II.	5½	1905	4200	2295	16·03	5·90	Rickets.
94	+ 10–20 g. yeast.	5½	1590	5000	3410	23·05	11·33	,,
95	,,	6	2410	6000	3590	18·02	9·75	,,
75	+ Malt ext.	4	3350	5240	1890	31·2	—	Normal.
86	,,	7	1810	4500	2690	18·68	12·64	Slight rickets.

TABLE V.—*Diet II. plus Different Fats.*

73	Diet II.	4	3950	6110	2160	20·7	—	Rickets.
71	+ 10–20 g. butter.	6	2150	6930	4780	29·04	15·5	Normal.
76	+ 10 c.cm. cod-liver oil.	9	2715	8000	5285	27·41	16·82	,,
80	+ 10 c.cm. linseed oil.	5	2535	6115	3580	16·22	8·08	Rickets.
81	,, ,,	5	2875	5320	2445	13·33	6·08	,,
109	+ 10 c.cm. peanut.	5½				26·35	15·60	Normal.
102	+ Wat. ext. of butter.	6				16·64	6·95	Rickets.

TABLE VI.—*Diet III. with Various Fats instead of Linseed Oil.*

138	Diet III.	3	1755	2685	930	16·58	7·14	Rickets.
140	,,	3	1060	2100	940	20·46	7·36	,,
		Weeks.						
148	With cod-liver oil.	17	1735	3890	2155	27·78	16·51	Normal.
146	With butter.	17	1920	3765	1845	26·95	15·89	,,
147	With olive oil.	17	1445	2625	1180	23·79	13·22	Slight rickets.
163	With peanut.	17	2350	4020	1670	18·88	13·81	,,
145	Diet III.	17	1830	3605	1775	21 60	12·35	Rickets.

TABLE VII.—*Diet III. Plus Meat and Meat Extracts.*

141	Diet III. + 5 g. meat.	17	2490	5820	3330	17·48	7·19	Ricket .
143	+ 20 g. meat.	17	2890	4400	1510	17·88	9·48	,,
144	+ 50 g. meat.	17	3690	8825	5135	15·74	10·72	,,
160	+ Watery ext. of 50 g. meat.	12	2005	3825	1820	13·88	7·20	,,

Using Diet I., we see in Table II. that increasing the whole milk from 175 to 500 c.cm. per diem prevents the development of rickets. In other tables are experimental results obtained by means of Diet II.

On Diet II. not only does meat but both the watery and alcoholic (80 per cent.) extracts have an inhibitory effect. (Table III.) On the other hand, the protein residue after loss of extractives allows rickets to develop.

Table IV. shows the effect of adding malt extract and yeast to Diet II. Yeast therefore has no protective influence. Malt extract has some inhibitory action and delays the onset of rickets when added to Diet II.

A large number of experiments were now made in which the effect of different fats were analysed. A few of the results are given in Table V. Many other fats and margarines, animal and vegetable, were tested, but almost uniformly they prevented rickets, the only undoubted exception being linseed oil. The results allowed the evolution of Diet III., in which separated milk was used in order to eliminate the milk fat, whose place was taken by linseed oil. Yeast was also added to the diet. Using this diet, a closer analysis of the effect of different fats was possible. (Table VI.) Now we see from the calcium results, which are an accurate indication in this case of the rachitic picture, that the value of the oils is graded, cod-liver oil being the best and linseed oil the worst; the vegetable oils, olive and arachis, are not so good as butter.

It was found that adding orange juice (¼ orange per diem) did not prevent rickets. Further, that the addition of 5 g. calcium phosphate, or doubling the separated milk and so increasing the calcium intake in this form was without preventive action on the development of the disease. In Diet IV., therefore, the separated milk was doubled and 3 c.cm. orange juice per diem also given. On Diet IV. the growth and general health of the puppies seemed better, and both these factors are of importance in such an investigation. Another improvement was to substitute 5 g. of yeast by a small quantity of a commercial yeast extract (3–4 g. per diem).

On Diets III. and IV. it was found that small quantities of meat and meat extract did not prevent rickets developing, as they have previously been observed to do when used in addition to Diet II. Table VII. illustrates some of these results. Although meat did not prevent rickets, a closer analysis of these and other results showed that it did have some inhibitory effect. It will be noticed, for instance, that the CaO present in the fresh femur shaft of Exp. 144, where 50 g. of meat was eaten, is higher than in Exp. 141, where only 5 g. of meat was added to Diet III. The action of small quantities of meat (10 g. per diem) is best seen when given with quantities or types of fat otherwise ineffective in preventing rickets. It will often be seen to keep the growth

normal, whereas in its absence rickets would develop. This, no doubt, explains the experimental results obtained when meat was added to Diet II. The small amount of butter—i.e., about 5 to 7 g.—in the milk of this diet had its anti-rachitic effect enhanced by the small amount of meat.

On Diet III. it was seen that the action of the fats as regards rickets was graded, the animal fats being more anti-rachitic than the vegetable fats and the latter differing from each other greatly. The best of the vegetable fats in preventing rickets are arachis (peanut) and olive oils. The worst of those examined include linseed, cottonseed, babassu oils, a hydrogenated fat, and cocoanut oil. These oils were all refined.

Importance of Dietetic Factor

The above dietetic results indicate that diet plays an important part in the etiology of rickets. An examination of the results obtained suggests that rickets is a deficiency disease which develops in consequence of the absence of some accessory food factor or factors.

Of the three factors known, fat-soluble A, water-soluble B, and antiscorbutic, two of these can be at once excluded. Yeast has no preventive influence on the development of the disease, and in consequence water-soluble B cannot be considered as of importance. Again, orange juice, sufficient to exclude any possibility of scurvy when considered with the rest of the diet, did not inhibit the disease, and this therefore allows the exclusion of the antiscorbutic factor. On the other hand, the anti-rachitic substances for the most part have been found, so far as the rickets experiments have gone, to be similar to those in which, according to the experiments on growth, of McCollum, Osborne, Mendel, and others, fat-soluble A is present. It therefore seems probable that the cause of rickets is a diminished intake of an anti-rachitic factor which is either fat-soluble A, or has a somewhat similar distribution to fat-soluble A. The facts are not all in favour of this hypothesis as it stands, and these will be discussed in the next lecture.

Another point which has been definitely established in the course of this work is that rickets develops much more readily in the fast-growing puppies than in those growing slowly. As might be expected, therefore, the prevention of rickets in a rapidly growing dog requires more anti-rachitic factor to keep the growth straight. This point is brought out in the case of two puppies of the same litter (Exps. 173 and 174) fed on the same diets (Diet IV. + 10 g. meat). The larger puppy grew much more rapidly than the other. Puppy (K) 173 increased from 1130 to 2240 g.—i.e., a gain of 1110 g. in 10 weeks, whilst L (Exp. 174) increased in weight from 1800 to 3970 g.—i.e., a gain of 2170 g. in the

same period. It will be seen in the X ray photographs that rickets is more strongly developed in the faster growing dog, although both are rachitic, the diets being deficient in the anti-rachitic factor. Puppies of the same litter which received 10 g. of butter in addition to the diets received by Nos. 173 and 174 were normal.

LECTURE II.

We saw in the last lecture the manner in which the experiments were carried out, together with some of the main results. Substances which had no preventive action on the development of rickets included separated milk, bread, the protein of meat, yeast, linseed and babassu oils, and hydrogenated fat. Substances with well-marked preventive action included cod-liver oil, butter, and suet. Then there were other substances whose preventive action was definite but not so great as that possessed by the above animal fats. In this group were meat, meat extract, malt extract, lard, arachis and olive oils.

The Part Played by Fat-Soluble A.

The results seemed to favour the hypothesis that experimental rickets can be prevented by diets containing an abundance of anti-rachitic factor and that the anti-rachitic factor and fat-soluble A have somewhat similar distributions. There are, however, several points which are not in harmony with the ordinarily accepted views about fat-soluble A. Three of these will be discussed.

Relation of Rapidity of Growth to Development of Rickets.

Rickets develops best in rapidly growing animals, this fact being in harmony with the clinical observation that large and rapidly growing children most often suffer from rickets, whereas marasmic children generally escape. It is, therefore, difficult at first sight to associate a disease of rapid growth with a deficiency of fat-soluble A which is, according to accepted teaching, necessary for growth. For it has been shown, in the case of rats by McCollum, that both fat-soluble A and water-soluble B are essential for growth. Before fat-soluble A and the anti-rachitic factor can be held to be the same thing, further consideration is necessary.

The first point to emphasise is that some of the fastest growing dogs in these experiments have had very little fat-soluble A in their diet. Here are two examples :—

	Exp. 144.	Exp. 175.
Diet III. + 50 g. of meat per diem ...	—	—
Initial weight	3690 g.	—
Increase in weight in 13 weeks	5135 g.	4585 g.
Rickets	Marked	Very slight.

If the milk were completely separated, Diet III. ought to have contained no fat-soluble A. Meat is reputed to contain little or no fat-soluble A when devoid of fat. The fat was dissected off as completely as possible, but there was undoubtedly a little not removed.

The following experiments show that when only 10 or 5 g. of meat were added, or even without any meat, good growth was obtained.

In experiments 186 and 185 no meat was present in the diet and yet the puppies grew considerably, though, it is true, not to quite the extent of Exp. 190 where the fat eaten was cod-liver oil, which is known to contain fat-soluble A.

—	Exp. 176.	Exp. 141.	Exp. 186.	Exp. 185.	Exp. 190.
Diet	D. III. + 10 g. meat.	D. III. + 5 g. meat.	D. IV. (Linseed oil).	D. IV. (Olive for linseed).	D. IV. (Cod-liver for linseed).
Increase in weight ...	2930 g. in 10 weeks.	2720 g. in 10 weeks.	1200 g. in 5 weeks.	1100 g. in 5 weeks.	1525 g. in 5 weeks.
Condition ...	Rickets.	Rickets.	Rickets.	?	Normal.

These results cannot fail to raise the question as to the necessity of fat-soluble A being present in the diet before growth is possible. As the experiments were not carried out from the point of view under discussion I do not naturally deny that fat-soluble A is necessary for growth, more especially as the separation of the milk in the diets was not always perfect. I think, however, that it can be definitely stated that the amount of growth a puppy experiences has no relation to the amount of fat-soluble A in the diet, although a small minimum amount may be necessary. It is, of course, possible that puppies can make use of considerable stores of fat-soluble A in their own tissues, which will allow growth for some months even in the circumstances of deficient fat-soluble A in the diet.

It has, however, been already pointed out in this work that large and rapidly growing puppies require more anti-rachitic factor to prevent the development of rickets. If, therefore, fat-soluble A and the anti-rachitic factor are identical the presumption is that the function of fat-soluble A in the diet of puppies is not so much to ensure growth as to promote correct growth; in other words, to keep the growth straight: and the greater the amount of growth in any period the greater is the amount of fat-soluble A necessary to keep it along normal lines. If this view is correct, then it can hardly be claimed that fat-soluble A is in any different category from the point of view of growth than the antiscorbutic factor, for, even in the

absence of this latter, the rate of growth diminishes and there is often rapid loss of weight.

The Action of Meat and Meat Extracts.

The second difficulty involved in considering the anti-rachitic factor and fat-soluble A as identical is the part which meat and meat extracts play in the development of rickets. It has been seen that, although when added to Diet II. these substances prevent rickets, in the case of Diet III. rickets develop. Yet even in the Diet III. and IV. experiments, the action of meat is undoubtedly inhibitory in nature and, when 50 g. of meat are given, will almost prevent rickets in a small puppy. Just as in the last section it was seen that meat has a stimulating action on the growth of puppies far beyond its fat-soluble A content, so also it appears now that the anti-rachitic action of meat is in a greater measure than any fat-soluble A it is reputed to contain. Either we must recognise that meat contains more fat-soluble A than the rat-feeding experiments have led us to believe or we must endeavour to find another explanation of the action of meat in rickets. It seems to me that another explanation is possible.

It is known that meat has one action on metabolism, which is more strongly developed than in any other food-stuff. This is its specific dynamic action or power to stimulate the total chemical exchanges taking place in the body. In having this stimulating action it will increase the effectiveness of any fat-soluble A in the diet and will tend to prevent the storing up and deposition of this substance in the subcutaneous and other tissues. Again, any fat-soluble A in the tissues will be more readily mobilised under the stimulating influence of the metabolising meat. It is probable that the anti-rachitic action of meat may therefore be due more to its making the fires burn more brightly, and thereby increasing the effectiveness of any fat-soluble A present in the body, rather than to the fat-soluble A it possesses in itself. If this explanation of the action of meat be true, then it is still possible to regard fat-soluble A and the anti-rachitic factor as identical.

The Different Effects of Vegetable Oils.

The third difficulty, which is probably of less importance than the two foregoing, is the widely different action of the vegetable fats as regards the development of rickets. In the growth experiments of previous workers all the vegetable fats are described as deficient in fat-soluble A, and the impression is received that there is but little difference between them. On the other hand, their anti-rachitic

influence varies considerably, being obviously present in arachis and olive oils and absent in linseed and babassu oils. Other vegetable oils like cocoanut and cottonseed occupy an intermediate position. If the anti-rachitic factor is fat-soluble A, then it must be accepted that the type of experiment described in this work is a more delicate test for fat-soluble A than previous work involving the growth of rats.

The difficulties have now been stated and briefly discussed. On the whole, it will probably be agreed that they are not formidable, and not more than might be expected under the circumstances.

Since this is probably the first research on growth factors carried out on dogs, it might be expected that the facts would not be identical with those met with in rats. Again, a superficial survey of the question suggests that particular difficulties would be met with. For we know something of the part played by accessory food factors in such deficiency diseases as beri-beri and scurvy, and we know something of the part played by these substances in growth, but in the case of rickets we are apparently up against a combination of both a deficiency disease and growth, rickets, in fact, being a disease accompanying growth. Whether the anti-rachitic factor is fat-soluble A as previously understood is therefore undecided, but, on the whole, these substances appear to be identical. It is at least certain that the distribution of the two substances is remarkably similar.

Review of Some Earlier Hypotheses as to Ætiology.

It is interesting to see how the facts brought out in this work fit in with some of the most commonly held hypotheses of the ætiology of rickets. I think it will be agreed that the accessory factor hypothesis allows many of these older hypotheses to be so focussed that a common and simple image is visible.

Dietetic Hypothesis.

Rickets as a disease due to deficiency of fat.—The work of Bland-Sutton on the lion cubs at the Zoological Gardens has left its impress on English thought as regards rickets and, together with the acknowledged efficacious results that follow the treatment of rachitic children with cod-liver oil and other fats, has brought about a general acceptance of the view that rickets is due to deficient fat in the diet. The results recorded here make it clear why this view is so commonly held, but demonstrate that the efficacy of the treatment—curative or preventive (as regards the latter the work of Hess and Unger is of particular interest)—does not depend on fat *per se*, but rather on the type of fat, and

whether it contains an abundance of the anti-rachitic factor, animal fats being superior to vegetable fats.

Excess of carbohydrate in the diet.—When a diet contains excess of carbohydrate it means that it is made up largely of cereals. Now cereals, and more particularly cereals like wheat, rice, and oats, which have undergone transformation in the course of manufacturing processes, are most deficient in anti-rachitic factor. A diet, therefore, of such substances is quite unbalanced and most effective in producing rickets.

Deficiency of fat and excess of carbohydrate.—This condition comprises the first two hypotheses, and what is said about them can be extended with further emphasis to this suggestion. Such a combination would most certainly involve a deficiency of anti-rachitic factor.

Deficiency of calcium salts in the diet.—It has been seen previously that abundance of calcium in the diet, either in the form found in separated milk or in calcium phosphate, will not prevent rickets when the diet is deficient in anti-rachitic factor. Similarly, it has been found by some workers that a diet deficient only in calcium salts, but otherwise adequate, will not produce rickets. It is, however, more than probable that a deficient calcium intake associated with deficient anti-rachitic factor will bring about a more acute production of rickets, and must always be an adjuvant factor to be considered in the ætiology of rickets.

The "Domestication" Theory of Rickets.

Von Hansemann's "theory of domestication" includes in a comprehensive way all the unhygienic conditions associated with life in civilised and more particularly in crowded communities. The difficulty is that we have not yet complete knowledge as to what is unhygienic in the environment of civilisation. There is something subtle about the problem, and many of the factors about which we hear so much may be of little or no importance when compared with factors about which nothing is at present known. Modern mode of life, and particularly of urban life, has involved two main changes in environment: (1) diet; (2) greater confinement and lack of fresh air. My experimental results have indicated that the dietetic changes are of prime importance in bringing about the widespread development of rickets, although, according to the researches here described, diet must be considered from an entirely new point of view.

Effects of Confinement.

At this point I wish to consider the part played by confinement in the ætiology of rickets, more particularly because in recent years the experimental work of Findlay has indicated that it may be of importance. Findlay's work involved the use of 12 dogs fed on a diet of oatmeal porridge and milk (amount not stated). It will be seen that this diet is similar to Diet I. used in my experiments, a diet which normally produced rickets in experimental puppies. (Diet I. was composed of whole milk 175 c.cm., oatmeal and rice, and 1–2 g. NaCl.) On this diet, then, the confined dogs were rachitic, the dogs obtaining exercise normal.

It seems to me that, working with such a diet, which approaches a rachitic diet, experimental results can only show that want of exercise is a factor in the production of rickets, but cannot be regarded as proof that it is the primary factor. Before the acceptance of this hypothesis is possible it must be shown that confinement on an adequate diet—that is to say, one compatible with the best health, always brings about rickets. Certainly the porridge and milk diet, unless the milk is large, cannot be considered healthy (in three months two of Findlay's confined puppies died of broncho-pneumonia and one of marasmus).

The beneficial effect of freedom in the case of dogs on an inadequate diet is what might be expected and is not, in my opinion, discordant with a dietetic hypothesis. The constant movement must raise the whole metabolic changes in the body and, in the first place, prevent or delay the deposition of fat with its accessory food factor in the subcutaneous and other depôts and, secondly, bring into activity any anti-rachitic factor normally stored away and ineffective. Exercise, in other words, must give a greater opportunity to any anti-rachitic factor in the food or tissues of the animal to play its part in the animal economy. In addition to this, exercise or the possibility of exercise undoubtedly improves the animal's health, and it is almost certain that a rachitic diet is more effective in producing rickets when the animal's health is subnormal as it may be following continuous confinement.

A strongly rachitic diet after a few weeks has a decided effect on the animal's activity, and it is difficult to give any real exercise to a puppy that is rachitic even though the bony and ligamentous changes may not be the disability which limits the movement. On the other hand, confinement generally fails to prevent a well-fed puppy from taking abundant exercise. The analogy can probably be applied with greater force to children; a well-fed child between 9 months and 2 years can get exercise whatever its environment, whilst a child with active rickets will show the same

lethargy in a slum or the middle of Hyde Park. The activity of an infant is not to be measured by the amount of running it performs, but by its small movements.

My own experience is that confinement will not produce any symptoms of rickets in adequately fed puppies.

Results of Investigation in Glasgow.

It may not be out of place to refer to the recent statistical account of an investigation made by Miss Ferguson on rickets, more particularly in Glasgow. The results of this work are against the hypothesis that rickets is a dietetic deficiency disease and the general conclusion, although undetermined in a definite sense, is that the factors favouring the development of rickets are: (1) Insufficient space in houses; (2) confinement in such houses; (3) imperfect parental care. No support is given to the dietetic hypothesis. It is interesting, however, to examine some of the results relating to family budgets in this paper.

Below are given the tables relating to the "average consumption of food" (p. 68) in rachitic and non-rachitic families.

Now let us consider the tables, obtained by Miss Ferguson, in the light of the accessory factor hypothesis. First, what are the substances in the diets which allow rickets—i.e., are

Average Consumption per "Man" per Day of the Chief Articles of Diet in Grammes.

(1) Rachitic families. (2) Non-rachitic families.

—	(1)	(2)	—	(1)	(2)
Flour	387·9	376·2	Other cereals	15·6	26·9
Potatoes	291·0	236·8	Margarine or butter	32·6	38·5
Milk	256·0	309·0	Fish	15·7	35·9
Meat	89·1	92·6	Eggs	15·1	30·4
Sugar...	91·4	84·0	Cheese...	6·7	8·2
Oatmeal	40·4	36·0			

deficient in anti-rachitic factor? The answer is flour, potatoes, sugar, oatmeal, and other cereals. On the other hand, what are the anti-rachitic substances? Milk, meat, margarine or butter, fish, eggs, and cheese. The following table shows how the diets of rachitic and non-rachitic

families differ as regards these articles. The rachitic families received :—

Substances allowing rickets.	Substances delaying or preventing rickets.
11·7 g. more flour.	53·0 g. less milk.
54·2 g. ,, potatoes.	3·5 g. ,, meat.
7·4 g. ,, sugar.	5·9 g. ,, margarine or butter.
4·4 g. ,, oatmeal.	20·2 g. ,, fish.
11·3 g. less other cereals.	15·3 g. ,, eggs.
	1·5 g. ,, cheese.

Is it a coincidence that except as regards "other cereals" there is an increase in the diet of the rachitic families of the substances allowing rickets and, what is of greater importance, a decreased amount of substances having an anti-rachitic influence? It will, of course, be answered that the differences are too small in amount to be regarded as of importance. As a matter of fact, a moment's consideration will show that the real state of affairs is probably more emphatic than the figures represent. The outstanding fact brought out in Miss Ferguson's paper is that rickets is often associated with the more careless parents. It is clear that the infants below 2 years old will not get from such parents their proper share of the "good things" of the articles of the above budgets. The good things happen to be those substances containing the anti-rachitic factor. The children will undoubtedly be put off with an undue proportion of bread and the commoner foodstuffs which produce rickets.

It is improbable, however, that family budgets will ever decide the course of rickets in individual cases, but sufficient has been said to make it clear that in the appraisement and criticism of this statistical work too little attention has been given to this side of the problem and too much to the exercise and confinement factors.

General Consideration of Rickets as a Deficiency Disease.

It will be noticed that, although rickets has been interpreted on the basis of my experimental results as primarily a deficiency disease of a dietetic nature, this has not prevented other conditions from receiving attention and being considered as of some importance. A knowledge of general metabolism would not allow the exclusion of other factors; for dietetic problems must always be regarded as a whole, and the idea that accessory food factors can be considered separate and apart from other elements of the diet and from the general metabolism is unsound.

An adequate diet is itself a unit, and its soundness, to a large extent, consists of the mutual assistance and interplay in the metabolic changes the elements experience in the

body. The absence of, or deficiency in, one element means the ineffectiveness of another. For instance, the absence of carbohydrate involves a defective oxidation of fat, and probably an inefficient protein metabolism. Similarly, it is possible to imagine an abundance of accessory food factors in the diet which may, however, be ineffective because of some wrong balance in the energy-bearing materials. The same argument applies where the metabolism varies for reasons other than diet.

These few words are all the more necessary because recent work on accessory food factors has appeared too self-contained and, if persisted in, may be responsible for a period of disbelief in their existence with subsequent lack of progress in the study of a subject which is obviously of prime importance both from the academic and practical points of view.

The Dietetic Problem.

There is some danger in applying laboratory results to a clinical condition, more especially when the results are new and for the most part uncontrolled by clinical observation. But some remarks are necessary in this connexion, for, if experimental research can point to the real cause of a disease, then not only is the curative treatment controlled, but, what is of much greater importance in the case of rickets, it ought to be possible to indicate why rickets is widespread and to direct knowledge along preventive lines.

It appears, then, from this work that the foodstuffs of an infant ought to contain a maximum amount of anti-rachitic factor. Since, further, the dietetic problem is one of balance, foodstuffs which contain no anti-rachitic factor cannot be considered as neutral, but as positively rickets-producing, for the more of them that is eaten the greater is the necessity for foods containing the factor. Since there is a limit to what a child can eat, the inference is obvious. It is probable that bread is the worst offender, and to allow bread to form too large a part of an infant's dietary seems to me to be courting disaster. The same statement may apply to other cereals, but this has not been worked out to any extent.

Another point of importance is the type and amount of fat eaten by children. Since the above remark as to the limited amount of food a child can eat applies with even greater force to fat, it is necessary to give children the best fat from the point of view under consideration. They should therefore not be given vegetable margarines or any other vegetable fat. The natural fat for a child is the fat of milk, and to give it a vegetable fat not only limits the amount of butter it can eat, even if procurable, but also weighs down the diet in the rachitic direction. If additional fat is given to that normally eaten, then cod-liver oil is the best.

Milk as an Anti-rachitic Factor.

Undoubtedly milk ought to remain the staple article of diet not only until weaning, but for some years after this time. Milk is undoubtedly better than the corresponding amount of butter. Under normal circumstances the child would then be assured of a good supply of anti-rachitic factor. Not, however, under all circumstances is this certain, for the work of McCollum, Simmonds, and Pitz has shown that before an abundance of fat-soluble A appears in the milk the mother must have a good supply of this substance in her food. This means that the animal's power of synthesising these accessory food factors is small or absent. Grass is a good source of fat-soluble A for the cow, and a well-fed cow, from this point of view, will give good milk. The mother drinks this milk, and the accessory food factors are passed on to her mammary glands, thereby allowing the breast-fed child to get an adequate supply.

The problem therefore reverts largely to the feeding of the cow, and it is probable that the cow fed in the stall largely on vegetable oil-cakes will give a milk deficient in accessory food factors. If, therefore, a nursing mother's diet is deficient in the anti-rachitic factor, it is easy to understand how the breast-fed child develops rickets, for it is probable that the same argument applies even if it should subsequently prove that the anti-rachitic factor and fat-soluble A are not identical. Recently Hess and Unger have shown that the diet of the negro women in New York, whose breast-fed children are nearly always rachitic, is very often deficient in fat, the amount of milk they drink being small. These suggestions may also explain why rickets develops more commonly in the winter months, when the cow's diet is more artificial.

Other Foodstuffs.

As for the action of other foodstuffs, it has been pointed out that meat has an anti-rachitic effect to some extent and even in small quantities (10 g. a day to a puppy) will render a slightly rachitic diet safe, probably by making the anti-rachitic factor in the diet more effective. Vegetable juices seemed also to have some inhibitory action on the development of rickets.

In these days, when proprietary articles are so commonly used as foods for children, it is of vital importance that these substances should be judged by their accessory food-factor content in addition to the ordinary analysis as to any protein, fat, carbohydrate, and salts they may contain. Synthetic milks, especially such as contain linseed and other

vegetable oils, ought to be discountenanced as foodstuffs unless it can be satisfactorily shown that their accessory food factors are abundant. Similarly, the dispensing of vegetable oils instead of cod-liver oil to children, often rachitic when the oil is given, may do much more harm than good. This is most certainly the case, as I pointed out at the Physiological Society's meeting in January, 1918, when the type of Marylebone cream containing linseed oil is given. If children are to have the best chance for a healthy existence until further work extends or modifies my experimental results, it would be safer to exclude all vegetable oils from their dietary.

Finally, it is necessary to point out that this experimental work is far from complete, and no doubt in the near future much further knowledge will be forthcoming. The subject is of great importance and will not end with rickets. For instance, the researches of my wife on the action of accessory food factors on the development of teeth show how necessary it is that throughout the whole period of calcification of the teeth—i.e., up to the eighteenth year—there should be abundance of anti-rachitic factor in the diet, and a deficiency at any period will be reflected in the calcification and probable uneven arrangement of the teeth. Still further points of practical interest will come to light soon.

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