(b) Secondary dressings, when done, should be done in the operating room and aseptically.

(c) The injured part is not to be moved nor the wound surface to be damaged.

(d) Do not hesitate to employ anaesthetics for secondary dressings.

(e) Make late dressings as infrequent as early ones.

IMPORTANCE OF ROUTINE

In the further consideration of chronic osteomyelitis at this time it should be borne in mind that all forms of bone infection (in whatever manner they may have arisen) are under discussion. One of the too common teachings about chronic osteomyelitis, compound fractures, and, indeed, many other injuries and diseases, is that the surgeon and the method of treatment must adapt themselves to the individual patient, to the particular type of injury or disease, and to the circumstances surrounding the particular case. It is my definite opinion that such considerations interfere with proper treatment. In undertaking to develop a new method of therapy for these patients it was hoped that a plan might be found and systematized which would have a general application. It is my belief that such a plan has been found, and that the more nearly we can approximate a standard routine in dealing with these patients the better our results will be. We have learned that even bone and joint tuberculous patients with mixed infections will respond promptly to this plan of treatment, and in most cases go on in casts with infrequent dressings to as good a recovery as those who have been aspirated or drained aseptically. It is, of course, occasionally necessary to make departures for extraordinary conditions or circumstances. Speaking generally, however, it has been found possible to apply the plan of treatment described above almost without exception in dealing with all of these conditions. The prevalent notion that the individual patient and the individual surgeon must always have particular and different consideration for every case has been one of the commonest reasons for departure from established principles of treatment, and is responsible for many poor results.

With regard to the details of treatment in my method I have had hundreds of letters suggesting that this or that phase of the treatment might be modified or omitted. To all of these I have made the same reply—that the more closely we adhere to all the details the better our results will be. During the early years of my work for osteomyelitis patients I was often persuaded to leave off casts or splints, to do more frequent dressings, or in other ways to vary from my usual programme. In such cases I found that I encountered exactly those difficulties that we were so anxious to avoid. Those who do vary from this programme are quite certain to find that their patients will have pain, swelling, local or general inflammatory complications, or delayed recovery in one way or another.

CONCLUSION

I submit this discussion for your consideration in the hope that we shall be able to add something to the wonderful progress in surgery already made by many distinguished members of this Association. To review briefly what I have endeavoured to bring to your attention: adequate surgical drainage of infected areas; the maintenance of such drainage without exposing the wound to further trauma and infection; and prolonged protection of the wound, the injured or inflamed part, as well as the patient, against the evil effects of irritative motion, contracture deformity, and ultimate disability. These are all important functions of the attending surgeon. By such a programme the vital resources of the patient may not only be conserved but employed toward his recovery, limbs and lives may be saved, and the patients made more comfort-

able. They can also be taken care of at less trouble and expense than usual. If we have made progress in these directions we have made a definite contribution to this department of surgery. These features of surgical treatment and clinical results are difficult to study or to demonstrate in figures and statistical tables. We have had very few satisfactory reports of clinical results in osteomyelitis and compound fractures from our civilian clinics and hospitals. A study of the results obtained in wound infections and compound fractures from our military experience of fifteen years ago revealed many unhealed wounds, ununited fractures, and chronic infections years after the war was over. Similar figures from our civilian hospitals would show similar results. Suffering, meta-static infections, contracture deformities, incapacity for former occupations, and disability because of persistent pain do not appear in the statistical tables. I believe that we have been able to show, however, that with the simpler surgical therapeutic method I have described we have made definite improvement in these respects. Such clinical results can only be observed and recorded in general terms by surgeons and their associates on the basis of contact with patients and clinical experience. It is hoped that the plan which I have proposed will be given a trial. It is only upon the basis of such a special test that conclusions which are fair and which are scientific in the best sense may be reached.

[Lack of space makes it impossible to print here Dr. Winnett Orr's case records and statistical tables. For the same reason the author's account of correspondence and discussions, relating to the method of treatment, and giving the experience of other surgeons, has been omitted. This additional material will be found in a reprint to be published separately.]

THE SIGNIFICANCE OF VITAMINS IN PRACTICAL EXPERIENCE *

BY

LESLIE J. HARRIS, D.Sc., Ph.D.

MEDICAL RESEARCH COUNCIL'S NUTRITIONAL LABORATORY, UNIVERSITY OF CAMBRIDGE

The task I have set myself to-day is to summarize certain evidence as to the real practical importance of vitamins in day-to-day clinical experience. First, however, I want to say how fully I appreciate the great honour which your president has paid me in asking one whose work has lain principally in the laboratory and not in the clinic to open this discussion. But let me add this, that it would be a mistake to suppose that the research worker is not interested in the immediate practical problems of the clinician. At the same time, I am only too well aware that many practitioners still regard vitamins as largely of academic interest, and suppose that correct feeding is a matter that can be left to "Nature," or "instinct," or "common sense."

If one is asked, How did our ancestors manage to get on so well before the era of vitamins, I think one can only reply that they did not. In 1730 out of all babies born in London 74 per cent. died before they were 5 years old; in 1770 the figure had been reduced to 50 per cent.; and by 1833 to 30 per cent. During the first quarter of the present century the death rate of infants under 1 year fell continually and steadily, from 150 per 1,000 to 70 per 1,000. It would of course be unfair to minimize the important part played by other

* Read in opening a discussion in the Section of Diseases of Children at the Annual Meeting of the British Medical Association, Dublin, 1933.

factors, notably hygiene, in bringing about this wonderful improvement; only it does seem certain that another most important contributing cause has been the growth of the infant welfare movement, with the general adoption of improved methods of feeding. Next, what about relying on the free choice of natural foods, or on instinct? The futility of this idea becomes at once apparent when we recall that in our northern climates, particularly in many industrial districts, some degree of rickets has been almost universal—in the well-to-do classes, able to afford the proper "choice," no less than among the poor—and that no common foodstuff, not excluding milk itself, contains sufficient of the antirachitic vitamin to secure certain protection from rickets (assuming, of course, the child not to have the benefit of exposure to ultra-violet rays, in which our climate is so deficient).

Prolonged experiments carried out in my laboratory over a course of years^(a) indicate that, contrary to the popular idea, animals have no general ability to distinguish by instinct between a diet containing and one lacking some essential dietary constituent. Only when the constituent in question produces some quite immediate beneficial response does the animal learn to discriminate in its favour. Since the effects of most dietary deficiencies are of gradual development and the protective food produces no sudden dramatic improvement, any ability to discriminate is in such cases quite out of the question, although the final result of the deficiency may be just as disastrous and often indeed fatal. Similarly, we have no evidence that a baby developing rickets acquires a special longing for cod-liver oil.

While it may be admitted that in this country certain vitamin deficiencies, such as beri-beri or pellagra, are of no immediate practical concern, it must be borne in mind that medicine knows no national boundaries, and it would be wrong to shut our eyes to the facts that no fewer than 30,000 individuals died from pellagra in one year recently in the southern parts of U.S.A., and that in the East beri-beri (including infantile beri-beri) claims its victims almost by the million. Both these diseases, like rickets, are now readily preventable by dietetic measures. The problem, in short, has become one for the administrator, the economist, and the sociologist as much as for the laboratory worker. The first point I wish to consider in detail is the prevalence of rickets, to show that it is almost inevitable unless special prophylactic measures are taken and to discuss the most suitable methods of therapy.

PREVALENCE OF RICKETS

In 1868 Gee¹ concluded that one-third of the school children of London were suffering from rickets, and in 1871 a similar figure was given for Manchester.² It is important to note, however, that the incidence must in reality have been considerably higher than this, since such figures related merely to the more obvious and severe manifestations: the milder and earlier rachitic changes, now readily diagnosable by *x*-ray examination, would have passed unnoticed. Coming to more recent times and more modern diagnostic technique, Lawson Dick³ estimated in 1915 that no less than 80 per cent. of the children attending London County Council schools were rickety. Similar figures were given for Durham in 1920.⁹ Sir George Newman's official report in 1929 to the Ministry of Health¹¹ states that "an examination carried out in London schools of 1,635 unselected five-year-old school children revealed the presence of rickets in 87 per cent." Roughly 50 per cent. of the children examined from various parts of England⁴ showed some degree of rickets. Similar figures can be cited for the United States of America,^{5 6 7 8} Germany,¹² France, etc.

With a slowly growing recognition of the absolute necessity of routine administration of an antirachitic agent

an unmistakable improvement is becoming apparent. The crippling deformities so common at the beginning of the century are now by comparison relatively rare. It may be argued that many of the "mild cases" of rickets, detectable only by *x*-ray examination, are in fact almost physiological at a certain age or so slight as to be of little practical significance. Even so, as recently as 1919 a census of 16,000 cases of crippling in elementary school children showed that 11 per cent. were due to rickets.¹³ I have not by me any very recent figures for comparison, but it is evident that there is still ample room for further improvement.

Incidence of Rickets with and without Treatment

In Table I are summarized the results of an experiment by Selkirk, Greenbaum, and Mitchell,¹⁴ which is but typical of many carried out by numerous authors, comparing the incidence of rickets in untreated and in treated infants.

TABLE I.—Incidence of Rickets in Negro Infants

Prophylactic Treatment	Total Number of Infants in Group	Number of Cases of Rickets in Group	Rickets, per cent. Incidence
Untreated	22	17	77
Cod-liver oil	45	20	44
Irradiation plus cod-liver oil	43	9	21
Irradiation	78	15	19

Such figures could be multiplied a hundredfold (more examples are given below: see Tables II, III, and IV), and a close study of similar recent surveys should convince the disinterested student that, in the absence of special prophylactic measures, "some degree of rickets" supervenes in a very large percentage of instances, with a not inconsiderable sprinkling of cases of "severe rickets." We need not enter here into a consideration of the conditions applying in sunnier parts of the globe, where the intensity of ultra-violet radiation is sufficient to replace the vitamin D of the diet, provided the child is put out into the sunshine. But even there confinement indoors, as in the rite of purdah, often defeats the climatic advantage; and again, the diet may be lacking in adequate calcium and phosphate, which are as necessary as the vitamin itself for protection from rickety defects.

TABLE II.—Prophylaxis of Rickets with Cod-liver Oil (after Gebhart, 1917)

Treatment	Percentage showing Rickets after Three Months
Cod-liver oil	29
No cod-liver oil	70

MERITS OF DIFFERENT PROPHYLACTIC METHODS

Since we know that rickets was prevalent at a time when all babies were breast-fed, it is clear that breast milk is in itself an inadequate and uncertain antirachitic agent. This is confirmed by experimental animal feeding tests, which show that there is surprisingly little vitamin D in either human or cow's milk. As a supplement for the bottle, egg-yolk was at one time tried,¹⁵ with a certain amount of success, but of course it is much less potent than cod-liver oil. The latter, although it has proved of immense value in the past, is in turn definitely inferior to the concentrated preparations of irradiated ergosterol now available (ostelin, radiostol, viosterol, calciferol tablets). The drawback to cod-liver oil is simply that it is sometimes difficult to reach a dose large enough to give complete protection without causing digestive upset

(Wilson¹⁶). Furthermore, different specimens may vary considerably in activity, whereas the "synthetic" preparation can be administered at a definite, accurately standardized level.

Many are the accounts which have appeared in the past few years emphasizing the advantages of irradiated ergosterol over cod-liver oil as a measure of wholesale prophylaxis (Table III), and a majority of workers are also agreed that it has been more completely successful than arti-

TABLE III.—*Prophylaxis of Rickets (after J. H. Hess and others, 1930)*

Treatment	Number of Infants	Result after 5-8 Months' Treatment	
		Number of Cases of "Severe" Rickets	Number of Cases of "Slight" Rickets
No treatment ...	34	9	10
Cod-liver oil—1-3 teaspoons to 2 tablespoons a day	44	2	4
"Vioosterol 100 D"—10 drops or less per day	6	0	6
"Vioosterol 100 D"—10-20 drops per day	63	0	0

ficial sunshine baths, irradiated milk, or other forms of treatment.^{17 18 19 20 21} Although there is no evidence of the prevalence of any widespread deficiency of vitamin A among the people of this country (and, indeed, milk fat itself is a fairly good source), there can be no harm, as a purely precautionary measure, in using a synthetic preparation in which vitamin A is present in addition to vitamin D ("adexolin," "radiostoleum"), in imitation of natural cod-liver oil, which, of course, contains both of these "fat-soluble factors."

Dosage of Irradiated Ergosterol

The question of the most suitable prophylactic dose is of some importance. According to the early experiences (1928-9) of György,¹⁹ Hess, Lewis, and Rivkin,²⁰ Sobel and Claman,²¹ and others, the amount needed for full protection appeared to be "0.5 mg. of ordinary irradiated ergosterol" a day. Now, of course, specimens of irradiated ergosterol vary in potency, and results are therefore more accurately expressed, not in parts by weight, but (as has only recently become possible) in terms of the international standard. We may take it, however, that this dose of 0.5 mg. would be equivalent to about 2,500 to 5,000 international units of vitamin D—rather a high figure. For a time—after the danger of hypervitaminosis was first realized—there was a tendency for the dosage recommended to be on the low side. Alfred Hess advocated a standard dose of 10 drops a day of "100 D" (official U.S. vitamin D preparation, with 100 times the antirachitic activity of the cod-liver oil of the American standard) as sufficient to prevent any fall in blood calcium or phosphorus in the first year of life, but later²² it was found advisable to increase the dose to 30 drops (equivalent to about 3,000 international units). J. H. Hess and co-workers²³ got inadequate protection with 10 drops or less ($\leq$ 1,000 international units), but complete protection with 10 to 20 drops (= 1,000 to 2,000 international units: see Table III). To prevent rickets in premature infants, May²⁴ thought it necessary to give as much as 45 to 60 drops of "100 D" (equal to about 4,500 to 6,000 international units of vitamin D) for the first ten weeks and subsequently 20 to 30 drops (= 2,000 to 3,000 international units). The *British Pharmacopoeia* (1932) suggested 1,000 to 3,000 units as the prophylactic dose for infants. On the other hand, Mellanby²⁵ found that 1,500 international units were quite sufficient to produce a relatively slow rate of healing in actual cases of rickets, although 3,000 units were more effective; and he considers 5,000 units to be the maximum really needed for a cure. Now it is most important, in order to avoid hypervitaminosis, not to exceed the adequate dose. There is evidence that 10,000 units is on the borderline for hypervitaminosis. Perhaps a wise compromise; therefore, until more extended reports become avail-

able, would be to suggest 1,500 units a day as the standard prophylactic dose (equivalent to about $4\frac{1}{2}$ teaspoonfuls of "good cod-liver oil"). This would apply to children of 1 to 2 years and upwards. For infants under 1 year—and there seems every reason to begin prophylaxis at an early age, say 6 weeks—the dose might start at 250 to 500 units and gradually increase to 1,500. Most cases of rickets occur in the second year of life, but everything is to be said for continuing prophylaxis for some years beyond, at least. Since the need for supplementary vitamin D seems less urgent after the second year, the dose might be kept constant at 1,500 units irrespective of the increase in body weight.

PUBLIC HEALTH MEASURES AGAINST RICKETS

From what we have already said it would appear that the administration of irradiated ergosterol is probably the most certain routine method so far available of preventing rickets. When dealing with the less intelligent class of parent, however, and also to save labour, there would seem to be some advantage in prescribing a food, such as "ostermilk" ("sunshine glaxo"), in which a standardized amount of the irradiated ergosterol has already been incorporated. Any possibility of hypervitaminosis is thereby ruled out. Another remedy is irradiated milk, but this promises to be of greater use in the future than at present, since the different preparations still vary considerably in their activities, some being relatively inactive and the different technical processes of irradiation not yet having been fully standardized. Coward²³ found that, taking the average for the different specimens of irradiated milk examined, no less than five and a half pints would be needed to provide the equivalent of a mere two teaspoonfuls of cod-liver oil. Satisfactory results, it is true, have been recorded by a number of observers in the last few years^{26 27 28 29 30} (see Table IV), but others^{31 32} find protection to be only partial.

TABLE IV.—*Irradiated Milk in Prophylaxis of Rickets (Schönen, 1929³¹)*

Diet	Number of Children	Number of Cases of Rickets	Per Cent.
Irradiated milk ...	51	0	0
No irradiated milk ...	99	24	25

Direct irradiation of the child (ultra-violet therapy), if undertaken on a large scale, has the disadvantage of involving excessive communal organization and expense, apart, of course, from the difficulty of getting the infants to the clinic and, as Hess has pointed out, the danger of spreading infection among them when they are there. Heliotherapy, obviously enough, cannot be relied upon as a prophylactic agent in our northern climate, certainly during the winter months. We have not yet referred to an important recent innovation, halibut-liver oil, which is superior to cod-liver oil in that it may contain some ten times more vitamin D, and can therefore be easily administered at a higher level of antirachitic potency. Extensive clinical records and comparisons are not as yet available; but it seems certain, at least, that results cannot possibly be better than those yielded by the accurately standardized, concentrated solutions of "synthetic" vitamin D. The same applies to preparations now obtainable of fish-liver oils fortified with added vitamin D. In America extended trial has already been made of "yeast milk" (that is, milk obtained from cows specially fed on irradiated yeast, and having a greatly increased antirachitic potency). This remedy is simple, and needs no co-operation on the part of the mother; but, on the other hand, the dosage cannot be very accurately standardized, and it is doubtful how general its use will become.

CURATIVE TREATMENT

For curative treatment irradiated ergosterol seems undoubtedly the method of choice, although it cannot be disputed that almost as good results seem often to have followed the combination of cod-liver oil with actinotherapy. As already indicated, the great advantage of irradiated ergosterol over cod-liver oil is that it can be given at so much higher a level of antirachitic potency. Cod-liver oil may sometimes prove nauseating and give rise to digestive disturbances, and, as statistics conclusively demonstrate, it frequently cannot be fed at a quite high enough antirachitic level to be fully effective. Further, its vitamin value may vary considerably from one specimen to another. It has been claimed³⁶ ^{36(a)} ^{36(b)} ^{36(c)} that cod-liver oil is more effective than irradiated ergosterol in protecting humans when fed at the same number of rat units. This, however, in no way affects the force of the above conclusions. The explanation of the actual result may be that an equal amount of vitamin D in cod-liver oil is more completely absorbed than when dissolved in medicinal oil.

That irradiated ergosterol is in fact tending to replace cod-liver oil in clinical practice is evident from a considerable mass of literature. Hess, Lewis, and Rivkin²⁰ ³⁵ reported that irradiated ergosterol was the most satisfactory method of treatment in use, and highly specific: symptoms of rickets disappeared very rapidly, even in cases in which cod-liver oil had previously proved effective; the healing action could be detected by the naked eye within fourteen days. Wilkes and co-workers³⁷ obtained cures in every instance, and often more rapidly than with cod-liver oil. Aidin³⁸ also concluded that irradiated ergosterol was more effective, simpler, and more economical than cod-liver oil or direct irradiation; Sobel and Claman²¹ stressed the speed of action and the benefit for infants with weak digestion who are unable to tolerate fat. Schaferstein³⁹ had unvarying success in a series of 315 prophylactic and 225 curative cases. Further clinical reports illustrating the value of irradiated ergosterol in curative treatment have been published from all over the world.¹⁷ ²⁶ ⁴⁰ ⁴¹ ⁴² ⁴³ A suitable maximum curative dose for severe cases of rickets, say for children 1 to 2 years of age, would appear to be 5,000 international units of vitamin D a day. In the case of children under 18 months, or with milder cases of rickets, this should be reduced to, say, 3,000 units. (The dosage of 5,000 units is equivalent to 0.5 mg. of "ordinary solid irradiated ergosterol," fifteen teaspoonfuls of "good" cod-liver oil, or about 50 drops of the American "100 D"—that is, a solution of irradiated ergosterol one hundred times as active as a standard cod-liver oil. One gram of calciferol (crystalline vitamin D separated from crude irradiated ergosterol) equals 4 grams of ordinary irradiated ergosterol, or 4,000,000 grams of "good cod-liver oil."

J. H. Hess and co-workers²³ of New York, after considerable clinical experience, advocated in 1930 a dosage of 10 to 15 drops a day of "100 D" for mild rickets and 30 drops for severe rickets (equivalent to about 1,000 to 1,500 and 3,000 international units respectively); no ill effects suggestive of overdosage were seen after six to eight months' administration at this and higher levels. György¹⁹ ⁴⁴ of Heidelberg at first recommended 2 to 3 mg. of irradiated ergosterol for severe cases of rickets, but later, after further clinical experience, the dose was reduced to 1 mg. a day (this being equivalent, as near as one can judge, to some 5,000 to 10,000 international units). Hess, Lewis, and Rivkin²⁰ found 1 mg. to be the adequate dose for an average case of rickets. Sobel and Claman²¹ give as optimum doses: for children under 1 year of age, 1 to 2 mg. of irradiated ergosterol in divided doses two or three times a day; and for children over 1 year, 3 to 4 mg. Since, however, definite ill effects due to hypervitaminosis have been recorded with 2.5 mg.²⁰ (equivalent to about 1,200 to 2,500 international units) and with 4 mg.,¹⁹

and there is independent evidence that 10,000 to 20,000 units is on the borderline of toxicity, it would appear safer to fix the maximum therapeutic (curative) dose not higher than 5,000 units (about 0.5 mg. of "ordinary irradiated ergosterol"). This is a little lower than the B.P. 1932 recommendation of 5,000 to 10,000 units. As already mentioned, Mellanby has more recently found that in practice 3,000 units is generally a sufficient dose. Fortunately hypervitaminosis seems less likely in actual curative treatment of rickets than in preventive treatment.

AVOIDANCE OF HYPERVITAMINOSIS D

Turning now to the question of hypervitaminosis, one finds that two extreme and opposite points of view are frequently put forward. The first is that the danger of hypervitaminosis is practically non-existent; the second is that in view of the great risk it would be safer to avoid concentrated preparations of vitamin D altogether. Taking the latter point first, and admitting the risk, I do not think that on reflection many would agree that the benefits of a remedy should be thrown away merely because of the possibilities of misuse. It is conceded that the cure of rickets is most certain and rapid, and the right dosage is most readily administered when a concentrated synthetic preparation (irradiated ergosterol) is used. The solution to the problem then, to my mind, seems to be to take care that the directions for dosage are accurately and strictly adhered to. One would not lightly abandon the use of strychnine, for example, because the effective dose happens to be close to the overdose; but, rather, precautions must be taken to prevent misuse. As to the precise amount to be given of any particular commercial preparation of irradiated ergosterol, I think that the directions actually set out by the manufacturers can usually be relied upon, as the materials are accurately standardized: only, once again let it be emphasized, it is advisable to insist that they be followed rigidly. It would be an advantage if the strengths of the preparations in international units were always declared and the number present in each dose as recommended. Also, doses ought to be stated in accurate measured quantities rather than as so many drops.

Those who argue that the danger of hypervitaminosis is virtually non-existent base their case on the observation that the lethal dose for a rat is as much as 100,000 times the minimal dose. This argument is misleading, as I have pointed out elsewhere,⁴⁵ and for two reasons. First, the overdose is 100,000 times the minimal dose (that is, the amount needed to produce any visible effect at all in severe rickets), which is by no means the same thing as the optimal or therapeutic dose. And, secondly, and more important, there are also differences between species to be borne in mind. Whatever may be the case for the rat, for the human the toxic is indeed quite close to the optimum curative dose. The human seems relatively much more susceptible than the rat: in spite of the great difference in body weight, the actual weight of irradiated ergosterol needed to produce hypervitaminosis is nearly the same for the human infant as for the rat. Toxic effects due quite definitely to hypervitaminosis have been recorded in human babies receiving 2.5 to 5 mg. a day of irradiated ergosterol, while according to the clinical data of the same observers,¹⁹ ²⁰ ²² ³⁵ the optimum prophylactic dose of the identical preparation is about 0.5 mg. and the optimum curative dose as high as 1 to 2 mg. (that is, about one-third of the toxic overdose), and even higher doses—dangerously high—have from time to time been recommended by other workers.

Nature and Instances of Hypervitaminosis

It was first noted in Germany, by Pfannenstiel,⁴⁶ that excessive doses of irradiated ergosterol were toxic to experimental animals, and the lesions produced were

examined by Kreitmair and Moll.⁴⁷ However, these workers were unable to account for the condition thus produced; in fact, the rapid loss in weight led them to suggest that the effect might be due to an increased rate of basal metabolism. The writer and his co-workers at the Nutritional Laboratory in Cambridge were able to show that the condition was characterized by raised blood phosphate and/or calcium, and this, together with the excessive calcification of the growing bone, accompanied by calcification in certain soft tissues, could be logically contrasted with the lowered blood phosphate and/or calcium and the deficient calcification which occur in vitamin D deficiency. Hence the condition could legitimately be described as hypervitaminosis,^{48 49 50 51 52} and it was shown, moreover, that it was due specifically to the vitamin D itself and not to some toxic impurity, as other writers had supposed. That the ill effects recorded clinically after exhibition of excessive amounts of irradiated ergosterol were due specifically to hypervitaminosis could not be doubted when one noted the nature of the symptoms, which were identical with certain features first recorded in experimental animals in our laboratory at Cambridge—namely, raised blood calcium or phosphate, overcalcification of bone endings, immense excretion of calcium salts in the urine, etc.

Hess, Lewis, and Rivkin,²⁰ giving 2.5 mg. of irradiated ergosterol a day, encountered what appear to constitute the first recorded cases of clinical hypervitaminosis. The abnormalities observed included three types of hyperphosphataemia, without apparent ill effects, and several cases of excessively calcified bone and of hypercalcaemia, two of the latter manifesting untoward clinical disturbances. György at Heidelberg relates a similar experience, using doses around 4 mg. of irradiated ergosterol. A single case of calcification in the kidney with fatal termination, apparently due to hypervitaminosis, was seen by Putschar,⁵³ and the following observations have also been recorded: three instances of renal lesions after vigantol⁵⁴; renal damage after three teaspoonfuls of vigantol taken in error during one day⁵⁵; raised blood calcium or phosphorus in normal children or adults given 5 to 10 mg.^{56 57 58}; and loss of calcium by way of the urine in normal children given very large overdoses.⁵⁹ A recent fatal case is that reported by Thatcher⁶⁰ at Edinburgh, who described typical calcareous deposits in the kidney.

MODE OF ACTION OF THE VITAMINS

It is often said that nothing is known of how the vitamins work. This is no longer quite true. Thus, taking the vitamins in alphabetical order, we know that the primary effect of a deficiency of vitamin A is to cause a characteristic abnormality in certain cell structures, especially of mucous membrane cells and nerve cells. In vitamin B deficiency, carbohydrate metabolism cannot proceed normally and lactic acid accumulates, which, as we have shown elsewhere, causes a slowing of the heart rate,^{61 62} and which in the central nervous system, as Peters⁶³ has worked out, is responsible for the convulsive symptoms. In vitamin C deficiency the primary failure is in the function of certain highly active cells—for example, odontoblasts, ameloblasts, etc.—and, as Fish and I⁶⁴ have shown, other changes observed are in reality merely secondary to this primary effect. Vitamin D, again, seems to have a more purely chemical action in relation to calcium and phosphate metabolism. Thus the effects of vitamins B and D appear to be most obviously “chemical” or “metabolic,” while those of A and C are at first sight more noticeably “cytological,” although one realizes, of course, that ultimately chemistry and cytology cannot be divorced in this facile manner, since the changes in the appearance of a cell are but the

reflection of fundamental chemical changes proceeding within and around it.

Elsewhere I have described experiments confirming a detailed theory as to the mode of action of vitamin D.^{45 52} The matter may be summed up as follows. Vitamin D causes an increased “net absorption” of calcium or phosphate (the two are mutually interdependent) from the intestine—that is, more calcium and phosphate are absorbed from the gut, or less are excreted back from the body into the gut. Thus the level of the phosphate and/or calcium in the blood rises and, as a purely secondary mechanical result of this, extra calcium phosphate is precipitated out into the bone. That is, the amount of calcification in the bone depends entirely on the amount of calcium and phosphorus in the blood: there is no fundamental error in the bone in rickets, but the fault is with the blood, and rickets is in this sense “a disease of the blood.” If the blood phosphate and calcium can be kept at the right level sufficient bone salt is put down and so rickets does not develop, or, if it is already present, healing is brought about. This reasoning explains why in vitamin D deficiency (rickets) one has an excessive loss of phosphate or calcium in the stools, a low blood phosphate, and, in some circumstances, low blood calcium—hence an inadequate deposition of calcium salts in the bone. Whereas, in contrast, with too large doses of vitamin D we get the reverse picture—increased absorption, hypercalcaemia and/or hyperphosphataemia, and a resulting excessive degree of calcification.

VITAMIN D THERAPY APART FROM RICKETS

The essential point to bear in mind about vitamin D therapy, it appears to me, is that its effect is to increase the assimilation of the food calcium and phosphate. Hence vitamin D is the proper remedy for infantile tetany, a nutritional disorder seen in association with rickets and due directly to the hypocalcaemia. Similarly, vitamin D is the specific for juvenile rickets and osteomalacia (adult rickets). Such conditions are rare in this country, but very prevalent in certain regions. In coeliac disease, since fats are not tolerated in the diet, it is particularly necessary to administer vitamin D (as irradiated ergosterol), as a safeguard against rickets. The so-called “coeliac-rickets” is not a pathological entity, as the work of Parsons^{65 66} and others has clearly shown. In the case of nursing and expectant mothers extra vitamin D is essential, not so much to protect the young (any direct action on the foetus or the milk is almost negligible) as to improve the calcium assimilation of the mother herself and help her to replace the large amounts of minerals lost to the child or in her milk. Renal (low calcium) rickets is a non-nutritional disorder, having its pathogenesis in a renal abnormality and defective excretion of phosphate in the urine, and is not amenable to vitamin treatment.

VITAMIN D AND THE PARATHYROID

The active principle of the parathyroid (parathormone) bears a superficial resemblance to vitamin D in its effect in raising the blood calcium. Certain of the symptoms of excessive dosing of the two are similar. On these grounds it has been supposed by many writers that vitamin D acts through the intermediary of the parathyroid. Again, infantile tetany has often been regarded as due to parathyroid deficiency, with the result that parathormone has been used in the treatment of this and similar conditions. I believe this point of view to be quite fallacious and such treatment a profound mistake, except, conceivably, in an emergency, where parathormone is permissible by reason of its immediate but purely symptomatic action. I have shown that parathormone, so far from having any

vitamin D-like effect, does not influence calcium or phosphate absorption in rickety conditions, but has in fact a definitely deleterious action, aggravating the underlying error, draining still further minerals from the impoverished bones, and causing a net loss to the body as a whole. As I have pointed out,⁴⁵ the reason for the similarity of the symptoms is simply that they are secondary to the hypercalcaemia which vitamin D and parathormone both produce, although by different mechanisms.

From a practical point of view in this country vitamin D is far and away the most important of the vitamins. I had hoped to give here some brief attention to the other vitamins, but exigencies of space have precluded it. I must therefore content myself by including in the following summary merely an abridged statement of my conclusions with regard to these other factors, and ask the reader who is interested in the exact evidence on which these conclusions are based to refer to the short article printed separately.⁶⁷

CONCLUSIONS

1. Correct nutrition cannot be left to instinct, or to the use of "natural unspoiled foods," or to a varied diet, or to a process of free selection.

2. Recent official reports show that no less than 80 to 90 per cent. of the elementary school population in London gave evidence of having had some degree of rickets, notwithstanding the decreasing severity of the disease as now met with.

3. Statistical data have been collected to show that, under our climatic conditions, unless special prophylactic measures are taken, "some degree of rickets" supervenes in a large percentage of instances with an appreciable proportion of "severe" cases, no common foodstuff containing sufficiently large amounts of the anti-rickets vitamin. Cod-liver oil has proved a sterling remedy in the past, but has the disadvantage that it may be impracticable to give enough to ensure full protection in every case. Experience shows that the most certain remedy is irradiated ergosterol. From a practical standpoint, however, it is sometimes an advantage to use a food (for example, a proprietary dried milk preparation) in which the requisite quantity of irradiated ergosterol has already been incorporated by the manufacturers. Ultra-violet therapy has also given good results, but it presents practical difficulties in the administrative direction for "wholesale" prophylaxis. Experience is limited as yet with halibut-liver oil, which is richer than cod-liver oil in antirachitic vitamin, and with fish oils reinforced with extra vitamin, but these promise to be of value for the future. The claims for irradiated milk and "yeast milk" are also discussed.

4. For curative treatment irradiated ergosterol is undoubtedly the method of choice; it can easily be given at a sufficiently high and precisely standardized level.

5. When administering irradiated ergosterol, however, it is essential to adhere strictly to the correct dose, since overdosage gives rise to hypervitaminosis. Contrary to what is often supposed, the toxic overdose for the human is close to the optimum therapeutic (curative) dose (only three to four times greater). The clinical evidence is reviewed, and a dose of 1,500 international units a day is provisionally recommended for ordinary prophylactic use, and 3,000 (or a maximum of 5,000 units) for curative treatment. Experience shows that smaller doses may be only partially protective. The minimal toxic dose for the infant is about 10,000 units. Further clinical standardization is needed.

6. The mode of action of vitamin D is discussed, and parathyroid treatment is condemned for infantile tetany and other conditions of calcium or phosphate deficiency arising from inadequate retention of food calcium and phosphate.

7. Vitamin A cannot be regarded as a general anti-infective agent. Although we have no evidence of any widespread deficiency of it in this country in any way comparable to that of vitamin D, it is still advisable to

ensure that diets are adequately provided with it. The offspring receives but a moderate amount pre-natally and in the milk.

8. The effect of extra vitamin B added to the infant's diet requires further study. There is no compelling evidence to support the suggestion that the prevalence of constipation and stasis is due to lack of this factor.

9. It is essential that all infants should be dosed with adequate vitamin C (as orange juice). This is destroyed to a greater or less extent during pasteurization of milk, which, however, is never a very active source.

10. Adequate nutrition is not possible for certain sections of the community under existing economic conditions; and much scientific knowledge of nutrition already won fails to gain sufficiently wide recognition or practical application.

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ON THE NERVOUS CONTROL OF ABDOMINAL BLOOD VESSELS AND VISCERA *

BY

D. T. BARRY, D.Sc., M.D., F.R.C.S.

PROFESSOR OF PHYSIOLOGY, UNIVERSITY COLLEGE, CORK

The problem dealt with in this communication is that concerning the role of parasympathetic and sympathetic systems in the regulation of muscular movements and of vascular conditions in the abdominal viscera. The method adopted for experimental investigation has been already described (*British Medical Journal*, 1933, i, 956). A statement made in that article was to the effect that cardio-inhibitor fibres may be found arising at a low thoracic level in the dog. Cannon apparently recognized this possibility, to judge from his description of the procedure of cardiac denervation. In man all cardiac branches are said to arise above the root of the lung. The present writer has twice unwittingly stimulated these fibres below the root of the lung in the dog, once with a fatal result.

VAGAL INTESTINAL CONTROL

When either vagus nerve is excited by a fairly strong current a balloon in most parts of the small intestine shows some degree of external pressure upon it, as seen by a single prolonged up-stroke of the tambour lever. This contraction may take place as a response to stimulation of one nerve only, or it may fail to occur on stimulating either nerve. There are portions of the intestine where one can predict to some extent which nerve is going to show the greater influence. Jacobi said that in the rabbit the intestinal motor effects of the vagus were confined to one side. In the dog one gets no indication of such a distribution. In this animal I have found that in the upper reaches of the gut the action of the left vagus is somewhat more pronounced than that of the right, while lower down there seems to be little difference, at any rate in certain parts. The distribution of the nerves is not uniform, and there is no sharp definition of areas of right and left preponderance. Kuré and his associates say that the numbers of parasympathetic fibres supplied to the intestine vary greatly in different dogs.

If one now proceeds to cut the splanchnic nerves the intestine will often be observed to enter immediately into spontaneous rhythmic activity, but, if not, one has only to repeat the vagal stimulus to elicit rhythmic activity, which ceases with the stimulus and can again be evoked by repeating it. The splanchnic nerve inhibits particularly the rhythmic action induced by the vagus, but the antagonism is seen in quantitative as well as qualitative respect (Fig. 1). In this figure the arrows indicate the points of excitation and show the positions of corresponding points in the records. Note that there is a reversal of the blood pressure change and increase of the intestinal and gastric responses after splanchnic section. The observation points to the constant antagonism of splanchnic tone to vagal muscular impulses. Attention has recently been drawn by Jasper and Monnier and others to the rhythmic nature of the response to a single stimulus

of the crab's nerve. The well-known Ritter tetanus is a somewhat similar phenomenon. It is a feature which is masked in most simple responses. Here in the intestine is presented a good instance of masking and unmasking of the phenomenon. The fact that at a particular moment the quiescent intestine is induced by vagal excitation to enter into rhythmic activity, which ceases with or soon after the stimulation, suggests that the pneumogastric nerve is directly concerned with this form of activity, which is regarded by many observers as a purely myogenic process. Of course the evocative stimulus is iterative, but the serial contractions outlast it. From one point of view the phenomenon is not strictly comparable to that in the crab's nerve, which enables a single excitation to cause serial impulses.

Vagal contraction of the gut was annulled by atropine in two experiments before splanchnic section and in three experiments after section, and it was usually enhanced by injection of acetylcholine or pilocarpine, thus showing the true parasympathetic nature of the fibres concerned. Bayliss and Starling stated that large doses of atropine failed to paralyse the intestinal vagus, as they obtained contractions on stimulating the nerve after injection of large doses of the drug. Possibly the conditions in which those very accurate observers worked differed in some way from those of the present experiments, in which neither electrical excitation of the vagus nor acetylcholine produced any contraction after injection of atropine to the extent of 0.7 mg. per kilo. Possibly, too, we are at cross-purposes as between sympathetic and parasympathetic elements, the interrelations of which will be considered later.

In experiments performed with A. and B. Chauchard we determined the chronaxies of the gastric response and the vascular reaction (to be presently described) of the pneumogastric nerve. The gastric motor chronaxy is the greater,

FIG. 1.—Curves of stomach and intestinal contractions and blood pressure. Excitation of right vagus (r.v.) before splanchnic section in (A), and after section (s.c.) in (B). Reversal of effect on blood pressure. Time = 5 seconds in all records, and excitation period 15 to 20 seconds.

the capacity measuring 0.5 mF., which, with a resistance of 10,000 ohms, represents a chronaxy of 2.0σ as compared with 1.5σ for the vascular pressor response. Section of the splanchnic nerves determined a diminution of the gastric vagal chronaxy, which demonstrates the influence of a nerve on the property of excitability of its antagonist, the quantitative change being probably determined by some modification of the effector mechanism in the end-organ.

EFFECTS OF SPLANCHNIC EXCITATION

Stimulation of the cut end of the great splanchnic nerve produces inhibition of the gut, an effect which is presently increased by the influence of the adrenaline secreted. This is the generally recognized form of the splanchnic action both on stomach and on intestine, but an excitatory action is also in evidence, the converse picture of vagal inhibition, as is easily demonstrated by stimulation of separate bundles of splanchnic fibres. Two distinct types of activity are

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