Some Consequences of Overnutrition with Minerals

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It is difficult to know exactly what is meant by overnutrition. I assume we can eliminate such things as lead poisoning, but I am not sure whether chronic toxicity of essential minerals such as copper, iron or zinc is really any different from hypervitaminosis.

This topic is somewhat difficult because there are not many good clinical examples of overnutrition with minerals. Therefore, we will have to rely partly upon animal experiments and partly upon supposition.

Moreover, I find myself talking a great deal about overnutrition with calcium. This, in itself, is a little peculiar because nutritionists have spent the last twenty or thirty years vigorously promoting the consumption of higher levels of calcium throughout the world. In the United States, it is claimed that calcium deficiency is the primary nutritional deficiency in the population, that is, that some 30 per cent of the people in the United States fail to receive adequate amounts of calcium.[1,2] Now, if we do not have the highest intake in the world, we come very close to it; and if our nutritional status is poor because of low calcium intakes, I should think the rest of the world would have collapsed long ago.

On many occasions I have said that our nutritional standards for calcium are based on a false interpretation of the data. They are based on calcium balance studies which really give no indication of calcium need. They simply measure dietary habits.

Despite all the talk about calcium and the promotion of greater calcium intake, calcium deficiency, from the clinical standpoint, is still to be demonstrated. If it were a major problem, one might expect that calcium deficiency in many parts of the world would be very well defined clinically.

Of the things I have in mind that might be called overnutrition with minerals, perhaps fluorosis is the best example. The effects of high fluorine intake on teeth are well known. It is very unfortunate that the toxic effects of fluorine both in man and in animals were well known before the beneficial effects on dental caries were demonstrated. It is now well documented that when fluoride is added to water supplies at appropriate levels, with adequate control, there are absolutely no detrimental effects, and at the same time there is at least a 50 per cent reduction in dental caries. To me it seems practically criminal that so many people still fail to receive adequate amounts of fluorine because of opposition not based on scientific facts. Certainly, one of the efforts of all medical people should be to promote fluoridation wherever it is needed.

Another good example in animals is molybdenum toxicity. In certain areas of the world it has been shown that the molybdenum intake of various species is too high and that this promotes copper deficiency.[3] That is to say, in areas of high molybdenum intake a higher copper intake is required, or in other words, copper counteracts molybdenum toxicity. We do not know whether this has any implications in man. At least it is an example of an interaction between two essential nutrients, and perhaps more studies into the role of trace elements—studies that are only now beginning—will demonstrate relationships of this kind in human nutrition. Man is protected, to a considerable extent, from toxicities

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of this kind because his food supply is diluted out in the commercial market and usually comes to him from many areas rather than limited locations that have particular soil characteristics.

Another interesting example in animal nutrition that has been demonstrated only recently is zinc deficiency in swine. Ordinarily, a diet containing 30 to 40 parts per million of zinc is adequate for swine; but when the calcium level is raised to approximately 1 per cent, zinc deficiency develops, characterized by a severe parakeratosis.[3,4] It can be prevented, or cured, by either adding zinc to the diet or by decreasing the calcium in the diet. Again, we do not know whether this particular example is relevant to human nutrition, but it indicates some of the interrelationships that we may have to worry about. There is experimental evidence indicating that high calcium diets effect the utilization or requirement of several other minerals. These include iodine, iron, magnesium, manganese and, of course, phosphorus.[4,5]

With regard to calcium, perhaps the first thing that occurs to us is the relation of calcium to the hypercalcemia syndrome of infancy which has become so important recently in certain parts of the world. I suppose hypervitaminosis D is the most likely cause, although it still seems to be an inadequate explanation; and it is likely that high calcium intakes may be a contributory cause.

There is abundant experimental evidence to show that vitamin D toxicity, in animals at least, depends upon calcium intake. I think all studies on vitamin D toxicity have shown that high calcium diets increase the relative toxicity of vitamin D. We need, very badly, some quantitative evidence on the relative role of calcium and how important this may be.

The most important indication that calcium may be involved in idiopathic infantile hypercalcemia is that low calcium diets are of value therapeutically. For this word "idiopathic" it seems to me we should substitute "ignorance." It might help us in getting to the root of some of the problems we really want to know about.

Another area in which calcium may be involved is kidney stones. This possibility also has been demonstrated by a number of experimental studies, but the primary evidence would be simply that, therapeutically, low calcium diets seem to be called for. When a stone begins to form, it seems only logical to decrease the urinary calcium; one way to do this, of course, is to adhere to a low calcium diet. It seems to me that calcium intake cannot be the only etiologic factor in renal stones. There are many areas in the world where calcium intake is low but renal stones are common. I think we must assume that this is a complex etiologic problem of which calcium intake may be one facet.

In studies with animals in our department, we[6,7,8] have been able to show that on pyridoxine-deficient diets, the urinary excretion of oxalate is high. Under these conditions, with a high urinary level of oxalate, it is very easy to demonstrate that the calcium level in the diet is important and accentuates stone formation.

There is also some evidence in presumably well fed persons that treatment with pyridoxine will lower the excretion of oxalate.[8] Whether this indicates a pyridoxine deficiency or whether it is of relevance to kidney stones or oxalate stones in human beings, remains to be demonstrated.

Another area in which we might implicate calcium is in the milk-alkali syndrome. Again, this condition cannot be caused by a high calcium diet alone although it does emphasize that, under certain conditions, high calcium diets may be detrimental.

Many studies indicate that there are probably no universal nutritional standards and that the need for any particular nutrient depends upon many factors. We all know that physiologic function, growth, pregnancy and lactation, for example, are primary factors in influencing nutritional requirements. Numerous studies, both in animal and in human nutrition, indicate that various factors in the diet also influence nutritional requirements for others. Some of these I have alluded to, but there are many others that demonstrate that vitamin and mineral requirements are a func-

tion of the kind of diet and the level of intake of various other nutrients. Obviously studies are necessary in various parts of the world where the basic diets are different. It is doubtful that uniform standards will be satisfactory for all different nutritional conditions.

We have spent many, many years urging higher and higher intakes of various kinds of nutrients. In large part, this emphasis has been due to the so-called "margin of safety" that we allow to cover our ignorance. We all agree that people should not be kept on minimal levels of nutrition, but we have little scientific basis for estimating an adequate margin of safety. Also, it is time that we realized that the margin of safety must apply at the top as well as at the bottom in setting nutrition standards. Optimum nutrition, if I can define it, is somewhere in between too little and too much; and the definition of it really is our major problem in nutrition.

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DISCUSSION

Dr. Gilbert B. Forbes (*Rochester, New York*): Dr. Hegsted is the first speaker to mention the word "optimum" as applied to nutrition. I was happy to hear it used, although Dr. Hegsted admitted that he could not define it in precise terms.

There is one situation in human nutrition in which we can, with some degree of certainty, point to an optimum level of a dietary constituent. I refer to the work of Hodge* on fluoride intake in man (Fig. 1). As the intake of fluoride in the drinking water increases, there is a decline in the severity of dental caries; but if the intake rises above a certain level toxic symptoms, namely, mottled enamel, begin to appear. The junction of these two lines suggests that a level of one part per million in the drinking water provides an *optimum* intake of fluoride.

Perhaps if we had more such diagrams for other dietary essentials, we would be a little closer to a definition of optimum as it applies to nutrition in general.

Dr. L. E. Holt, Jr. (*New York, New York*): I would like to ask Dr. Hegsted if he thinks there is any place for molybdenum-iron in therapy.

Dr. Hegsted: When I first heard about this, I tried to look it up in the literature, and concluded it was a "gimmick"; I might be wrong.

Dr. Forbes: The term "hypercalcemia" was mentioned by Dr. Hegsted. Dr. Stapleton, do you have any comments on the infantile hypercalcemic syndrome and related problems?

Dr. Thomas Stapleton (*London, England*): Just a few thoughts occurred to me. First of all, it is a well known fact that among the people who were unfortunate enough to be prisoners in places in which there was not much food for them in the last war, those who started off as thin chaps survived better than those who started off as fat chaps.

In discussing calcium, Dr. Hegsted, I think it is frightfully important that one does not become too interested in just a mineral, because I am sure that the effects of the amount of calcium in the diet and the requirement for it depend very much on the protein intake of the individual.

Recently, we had a meeting to discuss and recommend the level of vitamin D fortification of infant foods in England; we chose 400 I.U. a day.† All I can say about the effects of our recommendation is that the British Paediatric Association this year is conducting a new survey of the incidence of hypercalcemia and of rickets in the United Kingdom and Northern Ireland. One hopes that at the end of the year the number of children with each disease will be equal; then one will consider that stating the requirement at 400 I.U. must have been a fairly reasonable figure.

Dr. Kurt Schreier (*Heidelberg, Germany*): I should like to mention only briefly that there is a disease called "Kaschin-Beck" syndrome around the Baikal lake area in Russia. Some investigators believe that it is due to overnutrition with iron.

Dr. Forbes: Dr. Harrison, do you have some comments on the calcium problem?

Dr. Harold Harrison (*Baltimore, Maryland*): I agree with Dr. Hegsted that the dietitians' and nutritionists' concern about calcium deficiency in this country seems highly overdone. It is hardly likely

* Hodge, H. C. The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. *J. Am. Dent. A.*, 40: 436, 1950.

† Editor's note: This represents a lower figure than that previously recommended, and it is of interest that the incidence of infantile hypercalcemia in Great Britain is now on the decline.

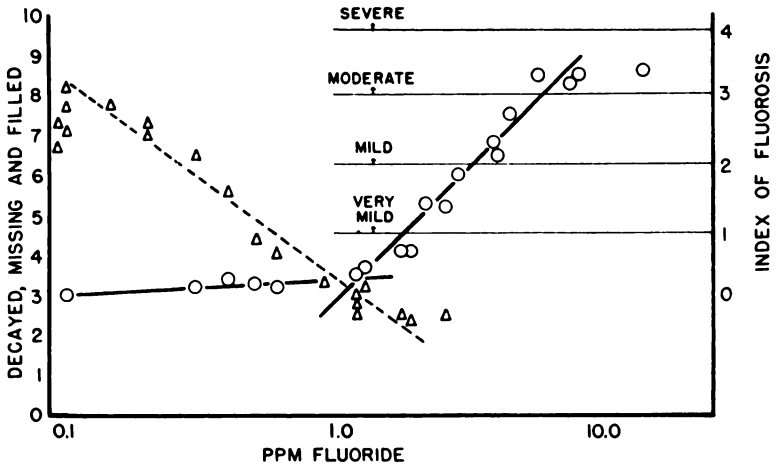

FIG. 1. Relation between water-borne fluoride, index of fluorosis and the number of decayed, missing and filled teeth. From: HODGE, H. C. *J. Am. Dent. A.*, 40:436, 1950.

that there is any serious calcium deficiency in this country. On the other hand, I am not convinced that the problem of overnutrition of calcium in this country has been demonstrated either. Certainly, high intakes of calcium are common, but all our evidence would seem to suggest that adaptation to such high calcium intakes, if the calcium is in the form of milk, is apparently good, and that when dysadaptation occurs, it is not because of the high calcium intake *per se*, but because of some other factor as in, for example, the milk-alkali syndrome Dr. Hegsted alluded to, or, perhaps idiopathic hypercalcemia. Some other factor has to be adduced besides the high calcium intake.

Perhaps we should look into such things as these: what makes adaptation possible, and why is adaptation to high calcium intakes no longer possible under certain circumstances.

DR. FORBES: I would like to ask Dr. Hegsted and Dr. Harrison if it is known why human breast milk contains so little calcium.

DR. HARRISON: This, of course, has been the reason why the National Research Council has been concerned about calcium requirements in infants, since, if they set up calcium requirements on the basis of balance studies, as Dr. Hegsted has pointed out, it would immediately rule out breast milk as a form of feeding for human infants. They tried to avoid this, however this does not necessarily prove that high calcium intakes are completely unphysiological for the infant. It may merely mean that the human mother cannot adapt to putting out such tremendous amounts of calcium in her milk as the cow. It may be that by the evolutionary process a nice compromise was reached, in other words, an amount of calcium which the mother could lose in her milk per day and yet just be enough for the human infant. It is not necessarily complete evidence that this is the optimal or the only type of calcium intake a human infant should have.

DR. HEGSTED: I do not really have anything more to add to what Dr. Harrison has already said, although I think you will find that the National Research Council did rule out breast milk as adequate by the calcium allowances. It was on the protein allowances that they failed to come to any agreement. However, the old allowances implied that breast milk was inadequate in protein for infants

I also would like to support what Dr. Harrison said, namely, that I am not very concerned about high levels of calcium intake. We do not really have much evidence that they are bad, except under certain conditions. I would like to emphasize, however, that we have just as much reason to worry about high intakes as we do low ones, particularly when we find intakes of the order of 3 and 4 gm. a day. This sounds high enough for me to be concerned.

DR. HERBERT SARETT (*Evansville, Indiana*): I would like to add to what Dr. Hegsted has said in connection with the availability of various minerals from different diets or foods. He gave some examples of this. These can be extended to include zinc, based on our experiments in chicks, in which the availability from soybean is much less than it is from casein. The manner in which the soybean is processed may also affect the degree of utilization of its zinc.

Therefore, in discussing dietary mineral requirements, the effect of different types of diets and different sources of the minerals must be taken into consideration.

DR. FORBES: There is one important dietary element which Dr. Hegsted did not mention which needs some comment. There has been a lot of talk recently about the relationship between sodium intake and hypertension in adult man, and some experimental work along similar lines in the rat. Dr. Darrow, would you comment on this matter? Are we feeding children too much sodium chloride?

DR. DANIEL C. DARROW (*Kansas City, Kansas*): I have nothing that is really relevant. I am not inclined to apply experimental data on rats or observations on sick children to healthy infants. Hypertension accompanying high intakes of sodium chloride is associated with desoxycorticosterone or presumably high production of aldosterone. However, the normal infant can handle the likely intakes of sodium chloride. I do not believe we ordinarily give foods containing harmful amounts of sodium chloride.

There has been a tendency to prescribe too much sodium chloride in heat stress and in diarrhea when obvious dehydration is not present. I think extra salt is seldom indicated in heat stress when the infant eats. While salt may be added to water when starvation is indicated to decrease stool volume in diarrhea, the concentration should probably not exceed 25 mEq. per L. It is not certain that these mixtures do not sometimes increase stool volumes.

DR. FORBES: Why does human breast milk contain so little sodium (only 7 mEq. per L. in contrast to 25 mEq. per L. for cow's milk)?

DR. DARROW: Obviously the human infant has survived on a low intake of sodium chloride for a long time. Human milk certainly provides an adequate intake. One may speculate that the low intake is, or was, advantageous during the period of adaptation to the environmental conditions of early evolution. The importance of sweat glands suggest a hot, relatively dry atmosphere but an environment providing water. Infant sweat is normally low in sodium and chloride. Consequently human milk provides sufficient sodium for high extrarenal losses of water containing little sodium.