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Dr. Malcolm Farrell
Fernald State School
Box C
Waverly 78, Massachusetts

Dear Dr. Farrell:

Dr. John W. Chamberlain has informed me of his preliminary conversation with you concerning the possibility of conducting a clinical study at your institution. He has requested me to give you further information as to the purposes of this investigation.

About thirty years ago, it was noted that when dogs were fed a diet high in cereal (notably oats) content, they developed a severe rickets. Subsequent research indicated that this effect was produced because cereals contain large amounts of phytates which form insoluble compounds with calcium that are not absorbable from the gastrointestinal tract. Thus, these cereals interfered with calcium utilization.

Phytates are hexa-phosphate compounds of inositol, a substance which has recently been shown to have vitamin activities. Chemical investigations have revealed that more than 50% of the phosphorus in cereals is combined in the form of phytates.

There has been considerable disagreement regarding the significance of phytates in nutrition, and the information on this subject is very confusing. Even though the data were not yet convincing, the British Government, during the recent war, added calcium carbonate to all flours in order to counteract the possible effect of phytates upon the metabolism of calcium in the British dietary. There is reason to believe that this precaution was unnecessary.

From time to time, nutrition experts and others have advised against the use of large amounts of cereal products in the dietary on the grounds that the phytates contained in these cereals interfere with

calcium metabolism. The poor of the world must eat diets high in cereal content. Thus, it is of considerable importance that we establish the significance of the effect of phytates upon mineral metabolism. We wish first to study the effect of phytates on iron metabolism.

In the past it has been difficult to measure the effect of a factor upon mineral metabolism because the techniques for measuring mineral absorption and excretion have been too crude. The recent production of radioactive minerals by cyclotron bombardment offers a new tool for the study of minerals. It appears that radioactive minerals are metabolized in exactly the same manner as ordinary minerals. Thus, it is possible to tag iron atoms, combine the iron into a compound, feed it and follow its metabolism in the body. Very minute quantities of radioactive substance are required, and the radioactive emanation from this substance is also extremely small.

The emanation is of the same physical character as cosmic rays and the quantities which we would give emit less energy than from the cosmic rays continually bombarding people living at the altitude of Denver, Colorado. This applies only to the regions where there are stores of iron in the body. In connection with blood preparations for the armed forces much larger quantities (3 to 5 times) of radioactive substances have been given to more than 100 medical students. Their blood was checked continually over a period of two years. There were no clinical signs attributable to this radioactive material. There is absolutely no ground for caution regarding the quantities of radioactive substances which we would use in our experiments. The fact that Dr. George Whipple has used these compounds in much greater quantities in his clinical investigations at the Rochester Medical School confirms this statement.

We had first planned to investigate the effect of phytates upon the metabolism of iron and calcium using rats. This would have been better because large numbers of animals could be used and extensive analyses could be performed on various tissues. Unfortunately, data obtained on rats would be of little interest in human nutrition for two reasons. The rat can utilize ferrous and ferric iron with apparently the same ease, whereas human subjects utilize ferrous iron two to twenty times better than ferric iron. Thus, rats differ from humans in their metabolism of iron. Secondly, there is present

in the intestine of rats an enzyme called phytase which has the ability to break down the phytate molecule, whereas the intestinal tract of human beings contains little or none of this enzyme. Thus, rats differ from humans in the manner in which they metabolize phytate.

Because we are interested especially in establishing the significance of phatates in human nutrition, it will be necessary for us to use human subjects. Since it has been shown that iron is absorbed by normal subjects most rapidly during the period of active growth, it is advisable that children be used as experimental subjects. Since human beings vary greatly in their metabolism of these substances, it is necessary that the same subjects be used for the entire series of experiments. Since the previous dietary has an influence upon the absorption and metabolism of minerals, it is important that the previous diet of all subjects used in an investigation be the same. Thus, the experiment requires that we use children who have been in the same institution for at least one month. In selecting the children, it is important that they have no disturbance or abnormality which would interfere with the metabolism of foods.

During the month of January, we propose to run an animal experiment using radio-iron so that we may work out our techniques and establish the procedure for the clinical investigation. It is not possible today to give you a detailed outline of the clinical procedure which we would follow. It is likely that we will want to give the subjects a vitamin supplement during the month of January to make certain that they have no malnutrition, for this might interfere with the absorption and metabolism of iron. On or about February 1, we expect to be ready to initiate the clinical experiment.

This experiment will be divided into five periods. On the first day of the experiment, we would give to each subject several micrograms of radio-iron in the form of ferrous sulfate in an aqueous solution. This feeding would be given early in the morning to subjects who have fasted overnight. Periodically during that day, we would take samples of blood (no more than 5 ml). During the next two or three days, similar samples would be withdrawn. The radio-iron content of the plasma and red cells of each sample would be determined. In this way we can obtain a record of the rate and amount of iron absorption.

After several days have elapsed so that the subjects will be stabilized again, the second period would be started on the same subjects. The second experiment is identical to the first except that a measured quantity of sodium phytate will be fed in the solution containing iron. Blood samples will be withdrawn and analyzed as before. This run will demonstrate the effect of sodium phytate upon the absorption of iron.

In the third period, the same amount of radio-iron will be administered and the same quantity of phytate will be given. However, the phytate will be fed in the form of rolled oats, corn or whole wheat bread. Blood samples will be withdrawn and analyzed as in the other two periods. This experiment will demonstrate the effect of phytates in food upon the absorption of iron.

In the fourth experiment, the same quantity of radio-iron will be fed and this time a diet consisting of the "average American diet" will be fed. Blood samples will be withdrawn and analyzed as before. This experiment will demonstrate whether the amount of phytate in the average diet has a significant effect upon the utilization of iron.

The fifth experiment will be a repetition of the first in order to establish whether the experimental subjects have changed during the period of the investigation.

We believe that these five experiments will take about eight weeks to complete if there are no unforeseen difficulties. In order that we may be certain that ten subjects complete the experiments, we should perhaps start with 15.

We are planning this investigation so that it will not interfere with the routine of your institution. If there is any way in which we can reward our subjects, we would be glad to do so. If the experiment can be carried out in your institution, we will be glad for any assistance which your medical staff can give us. Of course, we would recognize this assistance when the results are finally published.

We hope that this experiment can be carried out in your institution because the children there would be

ideal for this investigation and because you are convenient to the Massachusetts Institute of Technology laboratories where the analysis of blood samples will be carried out. Professor Robley Evans of our Physics Department is collaborating with us, and the radio-iron will be prepared in the M.I.T. cyclotron. I assure you that the results of this investigation will be of great importance and will influence our thinking in terms of the nutrition of mankind.

Sincerely yours,

Robert S Harris

Associate Professor of
Nutritional Biochemistry

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