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PROGRESS REPORT

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METABOLISM OF ^{90}Sr AND OTHER ELEMENTS IN MAN

April 1, 1976 to March 31, 1977
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RENEWAL PROPOSAL

April 1, 1978 to March 31, 1979

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The proposed work will be carried out on the Metabolic Research Ward of the Veterans Administration Hospital, Hines, Illinois, under the administrative supervision of the Loyola University Stritch School of Medicine, Maywood, Illinois.

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DATE: December 31, 1977

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This Progress Report covers the work conducted under Contract ER(11-1)-1231 for the 3-year Contract period July 1, 1973 to June 30, 1976, extended without additional funding for 21 months to March 31, 1978. The program for the proposed studies and the budget for the Contract period April 1, 1978 to March 31, 1979 are herewith submitted.

The proposed studies will be carried out in collaboration with the Environmental Measurements Laboratory, U. S. Department of Energy, New York, New York.

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I. ABSTRACT

Trace element studies of cadmium, copper, zinc, lead, manganese, and nickel have been carried out under strictly controlled dietary conditions in adult males during different calcium intakes. These studies are listed in Table 1. Complete metabolic balances of the trace elements listed above were determined in each 6-day metabolic period for several weeks by analyzing the constant diet and the urinary and fecal excretions of these "naturally" occurring elements, using atomic absorption spectroscopy. No additional stable or radioactive trace element was given. An intercomparison study of trace element analyses was carried out in five participating laboratories because of the known difficulties involved in the reliability, accuracy, and precision of the methodology of trace element analysis. The studies have shown that the cadmium balances were in equilibrium at all calcium intakes; the copper balances changed from equilibrium to negative values at higher calcium intakes. The nickel balances became somewhat more positive during the higher calcium intakes, while the manganese balances were positive at a calcium intake of 800 and 1300 mg per day. The lead balances were positive at all calcium intakes and became less positive as the calcium intake was increased. The zinc balances showed the expected pattern and most of the dietary zinc ingested was passed in stool. An additional study of four of these trace elements was carried out in collaboration with the Division of Radiological Physics, Argonne National Laboratory. The results of these studies are listed in Tables 14-24. Also, radiostrontium studies in man were carried out in the first year of the 3-year Contract period in order to complete previously initiated investigations. Publications and presentations of papers derived from studies carried out during the current Contract period are listed on on pages 64-66.

II. PROGRESS REPORT

A. Trace Element Studies

The difficulties in trace element analysis of human biological samples are well recognized. As a result of this problem widely varying results of trace element balances have been reported by other investigators[1,2]. In order to evaluate this aspect, samples of the diet, urine, and stool were sent for comparative trace element analysis of Cd, Cu, Pb, Mn, Ni, and Zn to several laboratories with considerable expertise in trace element studies. Table 2 shows the trace element analyses of biological samples obtained during a calcium intake of 1300 mg/day and Table 3 shows the comparative analysis of samples obtained during a calcium intake of 800 mg/day. These samples were analyzed in three laboratories. Each of these laboratories has assured us that their analyses, determined under strictly standardized conditions, are highly accurate and precise. However, the great variability of the results obtained is evident. The greatest differences were found in the analysis of lead, nickel, and cadmium of stool, of the lead analysis in the diet (one laboratory), and some smaller discrepancies in the analysis of nickel and lead in urine. All analyses were performed by atomic absorption spectroscopy. Table 4 shows values of the recovery of the various trace metals in diet, urine, and stool. Here again, marked discrepancies of the values are noted.

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1. Tipton, I. H., Stewart, P. L., and Dickson, J. Patterns of elemental excretion in long term balance studies. Health Phys., 16:455, 1969.

2. Price, N. O., Bunce, G. E., and Engel, R. W. Copper, manganese, and zinc balance in preadolescent girls. Amer. J. Clin. Nutr., 23:258, 1970.

The trace element balance data of four patients based on analyses which have been determined in one of the five laboratories are shown in Tables 5-8. Tables 5 and 6 show the trace element balance data determined during an 800 mg calcium intake per day and Tables 7 and 8 show the data obtained during a calcium intake of 1300 mg per day.

During a calcium intake of 800 mg/day (Table 5) the cadmium intake ranged from 7.7 to 13 µg/day in the five 6-day periods and averaged 10.24 µg/day. The urinary cadmium excretion was rather uniform in Patient 1 from one study period to the next and averaged 3.1 µg/day, while it varied in Patient 2 and ranged from 1.7-5.7 µg/day with an average 3.5 µg/day. Similar fluctuations of the urinary cadmium excretion were noted in Patient 3 in whom the excretions ranged from 1.2-7.5 µg/day in the five 6-day study periods with an average of 5.2 µg/day. The urinary cadmium of Patient 4 was very low in three study periods, less than 1 µg/day, while the values increased in the last period with a maximum of 8.5 µg/day. The average urinary cadmium of this patient is, however, not much lower than that of the other three patients. The fecal cadmium accounted for approximately one-third to two-thirds of the cadmium intake. These excretions fluctuated from one study period to the next, and these excretions fluctuated less than the urinary cadmium excretions. The average 6-day cadmium balances of each of the four patients ranged from negative to positive values but the overall average for all patients showed that the cadmium balance for the group was in equilibrium. The average fecal cadmium was twice as high as the urinary cadmium.

The copper balance data (Table 5) show that the intake was approximately 1000 µg/day and varied little from one study period to the next.

Most of the copper ingested with the diet was passed in stool, however, these excretions fluctuated from one study period to the next. In each of the four patients, the fecal copper excretion was unexpectedly high in one of the five 6-day study periods. The high fecal excretion of copper in these individual study periods were not associated with high excretions of any other trace metal studied in the same study period. These high individual fecal excretions resulted in a markedly negative copper balance in these specific periods, while the rest of the copper balances in the remaining study periods were slightly to moderately negative. These high fecal copper excretions in these periods contributed to high fecal copper excretions in the overall average for the group which resulted in a highly negative overall average copper balance of -567 µg/day (not shown in this Table). Since the high fecal copper excretions in these single periods under discussion grossly deviated from the values in the remaining four study periods, these unusually high values were omitted from the computation for the overall average for the group, however, for the sake of presenting all the facts, the unusually high fecal copper excretions are listed in Table 5. The corrected overall copper balance data show that the fecal copper was approximately 200 µg higher than the intake and the average copper balances for the individual subjects is negative as is the overall average for the entire group.

The zinc balance data (Table 5) show results similar to those previously reported, namely, that the main pathway of zinc excretion is via the intestine, while the urinary zinc excretion is low and ranged from 0.5 to 1.2 mg/day in the four patients and averaged 0.76 mg/day. In contrast, the fecal zinc excretoin averaged 11.5 mg/day during an average dietary zinc intake of 13.6 mg/day resulting in a slightly positive balance of 1.35 mg/day.

Table 6 shows data of the lead, manganese, and nickel balances of the same four patients during a calcium intake of 800 mg/day determined in the same laboratory. The lead intake in the five study periods ranged from 210 to 275 µg/day and averaged 243 µg/day. In all four patients the fecal lead excretions are low in relation to the intake and the average excretion ranged from 69.5 µg/day in Patient 7 to 96.8 µg/day in Patient 2 and the overall average for the group was +88.4 µg/day. The urinary lead of the four patients was rather uniform from one study period to the next and from patient to patient, and these excretions ranged from 27.4 µg/day to 41.3 µg/day and averaged 32.5 µg/day. Due to the low fecal lead excretions the lead balances of all patients were quite positive with an overall average of 122 µg/day.

The manganese balance data (Table 6) show that on an intake of approximately 2000 µg/day most of the manganese is excreted in stool. However, in some patients the fecal manganese was low, for example, in Patient 1 the average excretion was only 1367 µg and in Patient 7 it was 1480 µg/day, while the data of the other two patients showed the expected values for the fecal manganese excretions in relation to the intake. The overall manganese balances for all four patients showed that on an average dietary manganese intake of 2106 µg/day approximately 1750 µg/day were excreted in stool, the urinary manganese excretion was very low and averaged 5 µg/day and the manganese balance was positive, 351 µg/day.

The nickel balance data (Table 6) shows that the nickel intake was rather uniform in the different study periods, it ranged from 227 to 295 µg/day and averaged 259 µg/day. The fecal nickel excretion of two of the patients was only slightly higher than the urinary nickel excretion (Patients 1 and 7).

while in the other two patients (Patients 2 and 8) the fecal nickel excretion was approximately twice as high as the urinary excretion. Although the urinary nickel excretions fluctuated in the individual study periods the average urinary nickel excretion for the four patients were similar and ranged from 56.2 to 69.3 µg/day and the overall average for all patients was 62.7 µg/day. The nickel balances fluctuated greatly in the individual study period and the average balances for the four patients varied widely, from 28.6 to 114.5 µg/day and the overall average balance was 85.2 µg/day.

Table 7 shows data of the cadmium, copper, zinc balances determined during a calcium intake of 1300 mg/day in the same patients. In general, the fecal cadmium excretions were slightly lower in each case than during the 800 mg calcium intake, while the urinary cadmium was similar during the two calcium intakes. Due to the lower fecal cadmium excretion during the 1300 mg calcium intake, the cadmium balance was positive, 6.6 µg/day vs. -0.4 µg/day during the lower calcium intake.

The copper intake during the 1300 mg calcium intake (Table 7) was somewhat lower than during the 800 mg calcium intake, 700 µg vs. 960 µg/day, respectively. The urinary copper of Patients 1 and 2 were similar during the 1300 and 800 mg calcium intake, that of Patient 7 was slightly lower during the 1300 mg calcium intake, while that of Patient 8 was lower during the 800 mg calcium intake, 59 µg vs. 91.6 µg. The fecal copper excretions showed less fluctuations during the 1300 mg calcium intake than during the 800 mg calcium intake in all patients. The overall average fecal copper was considerably lower during the 1300 mg calcium intake, 643 µg/day vs. the corrected value of 1109 µg/day during the 800 mg calcium intake resulting in a less negative copper balance during the higher calcium intake, -47.5 µg/day vs. -324.8 µg/day during the 800 mg calcium intake.

The zinc balances determined during the 1300 mg calcium intake (Table 7) show that the zinc intake was approximately 1 mg higher than during the 800 mg calcium intake. The urinary zinc excretion of three of the four patients studied was very similar, about 0.7 mg/day, while that of the fourth patient was slightly lower, 0.39 mg/day. The fecal zinc reflected the intake and the overall average zinc balance was slightly positive, +1.45 mg/day. These balances are similar to those determined during the 800 mg calcium intake, the slightly higher zinc intake during the 1300 mg calcium intake was reflected by a correspondingly higher fecal zinc excretion.

Table 8 shows data of the lead, manganese and nickel balances determined during the 1300 mg calcium intake. In three of the four patients the average urinary lead ranged from 27.9 µg/day to 39.7 µg/day, while the urinary lead of one patient (Patient 3) was considerably lower, 10.5 µg/day. The overall average urinary lead excretion for the group was 28.5 µg/day. The fecal lead excretion of all four patients appears to be low and ranged from 85.6 to 136.5 µg/day with an overall average for the group of 113 µg/day. The lead balance of all patients was positive, averaging 87.5 µg/day. The lead balance data obtained during the 1300 mg calcium intake (Table 8) show that the lead balance was less positive during this calcium intake than during the 800 mg calcium intake (Table 6). This decrease of the positivity of the lead balance was due to the higher fecal lead excretion.

The manganese balances determined during the 1300 mg calcium intake (Table 8) show that the urinary manganese excretion is very low, with an overall average of 4.6 µg/day. The fecal manganese was very similar in

the four patients, averaging 1364.5 µg/day, resulting in an overall average manganese balance of +269.8 µg/day for the group. The manganese balances were less positive during the 1300 mg calcium intake than during the 800 mg calcium intake, taking into consideration the fact that the manganese intake was considerably lower during the higher calcium intake.

The nickel balance data determined during the 1300 mg calcium intake (Table 8) show that the urinary nickel excretion of three of the four patients studied was similar, and ranged from an average of 31.2 to 38.3 µg/day, while the excretion of one patient (Patient 3) was considerably lower, averaging 13.9 µg/day. The fecal nickel excretions varied and ranged from 86 to 123.6 µg/day. The overall average balance data show that the urinary nickel excretion averaged 30.1 µg/day, the fecal nickel excretion 107.7 µg/day, and the nickel balance averaged 113.7 µg/day. This nickel balance compares quite well with that determined during the 800 mg calcium intake, the main difference being a lower average urinary nickel excretion during the 1300 mg calcium intake, resulting in a slightly more positive nickel balance during the 1300 mg calcium intake than during the 800 mg calcium intake, +113.7 µg/day vs. 85.2 µg/day, respectively.

Table 9 shows data of comparative cadmium, copper, and zinc balances determined in three patients during a calcium intake of 800 mg/day and of 1300 mg/day. The cadmium balances of Patient 1 were similar during the two calcium intakes, while in Patients 2 and 7 the retention of cadmium was higher during the higher calcium intake. The copper balance data show that the urinary copper was similar during the two calcium intakes, while the fecal copper was lower during the 1300 mg calcium intake than during the 800 mg intake resulting in a positive balance in Patient 1 and in a less negative

balance in Patients 2 and 7 during the higher calcium intake. The zinc balance data show that the urinary zinc was approximately the same during the two calcium intakes and the fecal zinc excretion was also similar during the two calcium intakes except for the higher excretion in one of three patients during the higher calcium intake. The zinc balances became more positive in two of the three patients (Patients 2 and 7), however, the increase of the zinc intake by approximately 1 mg/day has to be considered.

Table 10 shows data of the lead, manganese, and nickel balances during the two calcium intakes of 800 and 1300 mg per day in the same three patients. The urinary and the fecal lead excretions of Patients 1 and 2 were similar during the two calcium intakes, while the urinary lead excretion of Patient 7 was lower and the fecal lead excretion was greater during the 1300 mg calcium intake than during the 800 mg intake resulting in a less positive lead balance of this patient. The lead balances of all three patients were less positive during the 1300 mg calcium intake than during the 800 mg calcium intake. The manganese balances (Table 10) show that the manganese intake was approximately 470 µg lower per day during the 1300 mg calcium intake than during the 800 mg calcium intake. The urinary manganese excretion was similar during the two calcium intakes. Despite the difference in manganese intake the fecal manganese excretion of Patient 1 was the same during the two calcium intakes, while the fecal manganese excretions of Patient 2 were in the expected range considering the low intake. In Patient 7 the fecal manganese decreased only by about 150 µg/day in the study carried out during the 1300 mg calcium intake, although the manganese intake was considerably lower in this study than during the 800 mg calcium intake.

It should be noted that the fecal manganese excretions of both Patients 1 and 7 were very low in relation to a manganese intake of 2100 µg/day during the 800 mg calcium intake. The manganese balance of all three patients became less positive during the higher calcium intake.

The comparative nickel balances determined during the two calcium intakes (Table 10) show the least fluctuations, although a decrease of the urinary nickel excretion is noted during the higher calcium intake.

Table 11 shows data of the cadmium, copper, and zinc balances of two patients who were studied during a low calcium intake of about 200 mg/day for five 6-day periods. The dietary cadmium intake averaged 10.3 µg/day. The predominant pathway of the cadmium excretion was via the intestine and the urinary cadmium excretion represented roughly one-third of the fecal cadmium excretion. In Patient 2 the urinary and fecal cadmium excretions fluctuated little except that the fecal cadmium excretion was higher in one 6-day study period than in the other study periods. The average cadmium balance of Patient 2 was negative, -1.7 µg/day, while it was slightly positive, +1.5 µg/day, for Patient 3 due to the lower urinary and fecal cadmium excretions.

The dietary copper intake varied little from one 6-day period to the next, averaging 897 µg/day (Table 11). The main pathway of the copper excretion was via the intestine, averaging 782 µg/day for Patient 2 and 718 µg/day for Patient 3. The urinary copper excretion varied little in the different 6-day study periods and the excretion values were similar for both patients averaging 90 µg/day for Patient 2 and 85 µg/day for Patient 3. The copper balances of the two patients were also similar, +25 µg/day for Patient 2 and was more positive for Patient 3, +94 µg/day.

The zinc balance data (Table 11) show that on an average dietary zinc intake of 14.8 mg/day the urinary zinc excretion was low and very constant from one 6-day period to the next. Most of the ingested zinc was passed in stool and the fecal zinc excretions fluctuated somewhat from one study period to the next. The zinc balance of the two patients averaged +1.3 mg/day and +2.8 mg/day, respectively, the difference in the zinc balance being due to differences in dietary zinc intake of Patients 2 and 3.

Table 12 shows data of the lead, manganese, and nickel balances determined during a low calcium intake of 200 mg/day. During an average dietary lead intake of about 210 µg/day the urinary lead excretion averaged 36 µg/day in both patients, the fecal lead excretion was low, averaging 42 and 49 µg/day, and the average lead balance of both patients was positive, +125 µg/day for Patient 2 and +132 µg/day for Patient 3.

The manganese balance data (Table 12) show that during an average dietary intake of 2232 µg manganese per day the urinary manganese excretion of both patients was very low, ranging from 6-18 µg/day and averaging 11 µg/day and 13 µg/day for the two patients, respectively. The fecal manganese excretions of the two patients differed considerably and ranged from 2100 to 2400 µg/day for Patient 2 with an average excretion of 2260 µg/day; for Patient 3 the fecal manganese excretions ranged from 928 to 1663 µg/day with an average of 1240 µg/day. Due to the marked difference of the fecal manganese excretions of the two patients, the manganese balances differed greatly and the manganese balance of Patient 2 was slightly negative, -39 µg/day, while the balance of Patient 3 was highly positive, +979 µg/day.

The nickel balance data (Table 12) show that the dietary nickel intake averaged 269 µg/day. Although fluctuations of the urinary nickel excretions

were noted, the average excretion of the two patients was similar, 164 µg/day and 133 µg/day, respectively. The fecal nickel excretions of the two patients differed somewhat, averaging 170 µg/day and 117 µg/day for the two patients, respectively, and the average nickel balance of Patient 2 was slightly negative, -65 µg/day and that of Patient 3 was slightly positive, +19 µg/day.

Examples of the calcium and phosphorus balances, determined during the different calcium intakes, are shown in Table 13. During a low calcium intake of an average of 229 mg/day the urinary calcium of one of the two patients was in the low normal range, 68 mg/day, while the calciuria of the second patient was very low, 11 mg/day. The fecal calcium approximated the calcium intake or slightly exceeded the intake and the calcium balances were slightly negative, -51 mg/day for Patient 2 and -27 mg/day for Patient 3. These negative calcium balances are normal for this low calcium intake. The phosphorus balance data show that the major pathway of phosphorus excretion is via the kidney, while the fecal phosphorus excretion was about half the urinary phosphorus excretion. The phosphorus balance was slightly positive.

During the normal calcium intake of an average of 791 mg/day (Table 13), the urinary calcium of the four patients studied was higher than during the low calcium intake and averaged 240 mg/day. The fecal calcium represented 76% of the calcium intake and the calcium balances of two of the four patients were in equilibrium and those of the other two patients were negative. The average calcium balance of the four patients was slightly negative, -53 mg/day. The phosphorus balance data show the expected pattern of the urinary and fecal phosphorus excretions and the average phosphorus balance was -62 mg/day, in agreement with the average negative calcium balance.

During an intermediate calcium intake averaging 1289 mg/day (Table 13), the urinary calcium of the four patients studied ranged from very low levels

of 22 mg to moderately high levels of 250 mg/day and the average urinary calcium of 149 mg/day was 100 mg lower than during the 800 mg calcium intake. This decrease is due to a combination of factors, i.e., the urinary calcium excretions of two of the patients studied during the normal calcium intake of 800 mg/day (Patients 1 and 7) was high and the urinary calcium of one patient (Patient 3) studied during the 1300 mg calcium intake, was very low. The fecal calcium during the 1300 mg calcium intake was greater than during the 800 mg calcium intake, as expected, and represented 83% of the calcium intake. The average calcium balance during the 1300 mg calcium intake was slightly positive, +64 mg/day. During an average phosphorus intake of 1542 mg/day (Table 13), the urinary phosphorus and the fecal phosphorus were 100 mg greater than during the 800 mg calcium intake, however, the increase in the phosphorus intake during the higher calcium intake, which was due to the addition of milk to the diet, resulted in a positive phosphorus balance, averaging +134 mg/day.

Collaborative Trace Element Study with the Division of Radiological Physics, Argonne National Laboratory

In addition to the trace element studies described so far, metabolic balance studies of cadmium, copper, manganese, and zinc were carried out in collaboration with the Division of Radiological Physics of Argonne National Laboratory. A total of 13 metabolic studies were carried out in nine adult males. Eight of the thirteen trace element studies were carried out during a low calcium intake of 200 mg/day, four during a normal calcium intake of 800 mg/day and a single study during a calcium intake of 1500 mg/day. These

studies are listed in Table 14. The analysis of the diet and excreta were performed by using atomic absorption spectroscopy. The analyzed dietary intake levels of cadmium, copper, manganese, and zinc in each 6-day metabolic period of the 90-day study are listed in Table 15.

Table 16 shows the mean values for the cadmium and copper balances during a calcium intake of about 200 mg/day. During a cadmium intake averaging 32.4 µg/day, the fecal excretion accounted for 65% of the intake, the urinary excretion for 48%, and the mean balance was negative, -4.5 µg/day. However, this balance did not differ significantly from zero. The copper balance data of the eight patients showed that the main pathway of the copper excretion was very low and corresponded to about 2% of the intake and the average copper balance of -36 µg/day did not differ significantly from zero. It should be noted that the cadmium balance in the first study of Patient 1 was negative, while the balance in a second study which was started several months later was positive. Similarly, the copper balance was also more negative in the first study than in the second study of this patient.

Table 17 shows the manganese and zinc balance data of the same patients during a low calcium intake of 200 mg/day. The manganese balance data show that on a mean intake of 2133 µg/day the fecal excretion reflected the intake, while the urinary excretion was low and corresponded to less than 1% of the intake. The mean manganese balance of -154 µg/day did not differ significantly from zero. The zinc balance data show that during a mean intake of 13.1 mg/day the major pathway of excretion was via the intestine. The fecal zinc excretion of 11.3 mg/day and the urinary excretion of 0.66 mg/day are in the expected range. The average zinc balance was positive, +1.14 mg/day.

Table 18 shows data of the cadmium and copper balances for four patients studied during a calcium intake of 800 mg/day. The mean cadmium balances were similar to those determined during the low calcium intake (Table 16). Similarly, the copper balances, determined during the 800 mg calcium intake, were also comparable to those determined during the low calcium intake of 200 mg/day (Table 16). The mean copper balance of -152 µg/day does not differ significantly from zero.

Table 19 shows the manganese and zinc balance data obtained during a calcium intake of 800 mg per day. The manganese balance data show that the average fecal excretion was about 300 µg/day higher than the intake and the average manganese balance was more negative than during the low calcium intake, -284 vs. -154 µg/day, respectively, but this difference was not statistically significant. The average zinc balances during the 800 mg calcium intake were similar to those during the low calcium intake.

Table 20 shows the mean values for the cadmium and copper balances determined during the various calcium intakes. On an intake of 32 to 35 µg cadmium per day the urinary cadmium excretion decreased slightly on increasing the calcium intake, the fecal cadmium excretions increased slightly but the cadmium balances were similar during a 200 mg and 800 mg calcium intake. In a single study carried out during a 1500 mg calcium intake the fecal cadmium excretion was greater than during the lower calcium intakes and the cadmium balance was slightly more negative. During all calcium intakes the cadmium balances were slightly negative and ranged from -2.9 to -5.2 µg/day. The copper balances were similar during the three calcium intakes, i.e., the fecal excretions were high, ranging from 1040 to 1160 µg/day, while the

urinary excretions were very low. The copper balances were slightly negative during all calcium intakes and they were more negative during the 800 mg and 1500 mg calcium intakes than during the low calcium intake of 200 mg/day.

Table 21 shows the manganese and zinc balances during the different calcium intakes. The manganese balance data show that the urinary and fecal excretions were similar during the three calcium intakes, the urinary excretions being very low, while the fecal excretions were slightly greater than the intake and the manganese balances ranged from -96 to -284 µg/day. The zinc balances were similar during the 200 and 800 mg calcium intake, the urinary zinc excretions were about 0.6 mg/day and the fecal zinc excretions reflected the intake, and the zinc balance was slightly positive. In the single study carried out during a calcium intake of 1500 mg/day the fecal zinc excretion was greater than the intake, resulting in a negative zinc balance.

The effect of a higher phosphorus intake, i.e., of 1500 mg/day vs. an intake of 800 mg/day on the metabolism of the four trace elements was studied in one subject (Tables 22 and 23). The cadmium and copper balances during the higher phosphorus intake (Table 22), show the addition of phosphorus increased the urinary excretion of cadmium and the fecal excretion of copper resulting in a more negative balance of both cadmium and copper.

The manganese and zinc balance data (Table 23) show that the high phosphorus intake resulted in an increase of the urinary manganese and of the fecal zinc excretion and both the manganese and zinc balances became more negative.

Table 24 shows data of the net absorption of the trace elements and data of the urinary excretions in relation to the intake of the respective element. The net absorption of cadmium was similar during the 200 mg and

800 mg calcium intake and was about one-half this value in the single study carried out during a 1500 mg calcium intake. The intestinal absorption of copper and of manganese was less during the 800 mg than the 200 mg calcium intake. During the 1500 mg calcium intake the net absorption of copper was in the same range as during the 800 mg calcium intake, while the absorption of manganese was lower. The absorption of zinc was lower during the 800 mg calcium intake than during the 200 mg calcium intake, while the absorption of zinc in the single study carried out during the 1500 mg calcium intake was similar to the absorption of zinc during the 200 mg calcium intake.

The urinary excretions of the four trace elements studied, expressed as percent of the intake (Table 24), show that the urinary cadmium excretion decreased with increasing calcium intake, while the urinary copper remained unchanged during the 200 and 800 mg calcium intake and was slightly lower during the 1500 mg calcium intake. The urinary manganese and zinc excretions were relatively unaffected by the calcium intake level.

The higher intake levels of the various trace elements in the study carried out in collaboration with the Division of Radiological Physics, Argonne National Laboratory, is most likely due to the fact that these studies were carried out at a different time than all other studies described in this report. The atmospheric fallout of particulate matter may have been greater at the time this collaborative study was carried out resulting in higher intake levels of the various trace elements.

The results obtained in this collaborative study compare well with those previously described in this report in terms of the cadmium and zinc balances, while the copper balances were in equilibrium and the manganese balances were

also in equilibrium or slightly negative. It should also be stated that the various trace element balances were quite consistent from one study period to the next.

The data obtained in this study were summarized and a paper entitled, "Metabolic Balances of Cadmium, Copper, Manganese, and Zinc in Man", was submitted for publication.

B. Radiostrontium Studies in Man

Although the main emphasis was placed on the study of non-radioactive trace elements, several studies of radiostrontium metabolism in man were carried out.

1. Effect of the combined use of orally administered ammonium chloride and of intravenous stable strontium on ^{90}Sr excretion in man

a. Background: The effect of orally administered ammonium chloride on increasing the excretion of ^{85}Sr in man has been reported from this laboratory in the past[1]. Also, the effect of ammonium chloride on ^{90}Sr excretion has been studied by this group in man[2]. Intravenous stable strontium has also been shown to increase the excretion of ^{90}Sr in man[3]. In view of these effects, the combined use of both of these compounds on ^{90}Sr excretion was studied.

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1. Spencer, H. and Samachson, J. Removal of radiostrontium in man by orally administered ammonium chloride two weeks after exposure: The effect of low and high calcium intake. Clin. Sci., 20:333, 1961.

2. Spencer, H., Samachson, J., Hardy, E. P. Jr., and Rivera, J. Effect of intravenous calcium and of orally administered ammonium chloride on strontium-90 excretion in man. Radiat. Res., 25:695, 1965.

3. Spencer, H., Samachson, J., Hardy, E. P. Jr., and Rivera, J. Effect of orally and intravenously administered stable strontium on ^{90}Sr metabolism in man. Radiat. Res., 51:190, 1972.

b. Results obtained with orally administered ammonium chloride and with intravenous stable strontium on ^{90}Sr excretion in man: ^{90}Sr and calcium balances were determined in control studies and during the oral administration of ammonium chloride, given for 6 days and stable strontium was infused intravenously on the last three days of the ammonium chloride administration. The dietary ^{90}Sr intake and the urinary and fecal ^{90}Sr excretions were determined in both study phases on aliquots of the diet, urine, and stool in each 6-day period. These analyses were determined by Dr. Harley's group using low level β-counting techniques[1].

Ammonium chloride induces metabolic acidosis which is associated with an increase of the urinary calcium. There was chemical evidence of metabolic acidosis in the patients studied, i.e., the plasma CO_2-combining power decreased in each case and the serum chloride increased.

Table 25 shows data obtained with ammonium chloride and with intravenous stable strontium on the urinary excretion of ^{90}Sr. In the control study the urinary ^{90}Sr excretion ranged from 0.20 to 0.85 pCi/day, in the ammonium chloride study the values ranged from 0.4 to 1.5 pCi/day and when both ammonium chloride and intravenous stable strontium were given the values ranged from 1.0 to 1.7 pCi/day. The urinary ^{90}Sr excretion increased by a factor of about 2 in the ammonium chloride study of the four patients.

Table 26 shows the ^{90}Sr and calcium balances of the four patients who received orally administered ammonium chloride and intravenous stable strontium. On a dietary ^{90}Sr intake of about 4 pCi/day in the control study the ^{90}Sr balance ranged from -1.1 to +1.1 pCi/day. In the experimental study the urinary

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1. Harley, J., Hallden, N., and Fisenne, I. Beta scintillation counting with thin plastic phosphors. Nucleonics, 20:59, 1962.

^{90}Sr excretion increased in all patients, the increase was about 2-fold in Patients 1-3 and 4-fold in Patient 4. The fecal ^{90}Sr excretions remained the same or decreased slightly in this 6-day period in Patients 1, 2, and 4, while it decreased markedly in Patient 3. This decrease may be due to delayed fecal passage of ^{90}Sr as the fecal excretion of calcium was also low in this 6-day period. In view of the fluctuations in fecal ^{90}Sr excretions from one study period to the next, it is difficult to interpret the ^{90}Sr balances and it appears that the main interpretation of the data rests on the changes of the urinary ^{90}Sr excretion. The urinary calcium increased in the experimental phase in all patients, the fecal calcium excretions are not interpretable as the calcium intake was greater in the experimental study than in the control study due to the calcium content of the enteric coated ammonium chloride tablets.

The data obtained indicate that ammonium chloride alone or used in conjunction with intravenous stable strontium increases the urinary excretion of chronically ingested ^{90}Sr and that this combined treatment is more effective than ammonium chloride alone.

A number of other studies of radiostrontium metabolism in man which have either been published or presented are described on pages

C. Short Description of Published or Presented Material

1. Studies of zinc metabolism in man

Studies of zinc metabolism were carried out in man under strictly controlled metabolic and dietary conditions. Metabolic balances of zinc were

determined for several weeks by analyzing the dietary intake of zinc and the excretions of zinc in urine and stool.

a. Studies of zinc metabolism in normal man and in patients with neoplasia

This study has shown that the amount of zinc necessary to attain zinc equilibrium is about 12 mg/day under normal conditions. The studies have demonstrated that the loss of zinc during weight reduction induced by a low calorie intake is as great as the loss of zinc induced by total calorie restriction during total starvation. These studies have also shown that the plasma level of zinc does not reflect the dietary intake of zinc nor the continued loss of zinc as the marked loss of zinc during weight loss was associated with an increase of the zinc plasma levels. During nutritional repletion or in a state of malnutrition, the zinc balance may be very positive for a prolonged period of time. The studies have also shown that the metabolism of zinc differs greatly in patients with certain types of neoplasia compared to that of normals.

This study has been published: Spencer, H., Osis, D., Kramer, L., and Wiatrowski, E. Studies of zinc metabolism in normal man and in patients with neoplasia. In: Clinical Applications of Zinc Metabolism. W. J. Pories, W. H. Strain, J. M. Hsu, and R. L. Woosley (eds.); Charles C. Thomas (publ.); Springfield 1974 pp. 101-112 (ENCLOSURE 1).

b. Certain aspects of zinc metabolism in man

Some of the results obtained in the studies of zinc metabolism in man were presented at the Fall Meeting of the American Physiological Society

in Albany, New York, August 1974. These studies emphasized that the main pathway of zinc excretion in man is via the intestine, that the urinary zinc excretion is low, about 0.5 mg/day, and that increasing the dietary zinc intake from 12 mg/day to 22 mg/day or lowering it to 7 mg/day did not alter the urinary zinc excretion. The changes in urinary zinc excretion, therefore, do not always reflect the zinc intake, while the fecal zinc excretions reflected the intake. The plasma levels of zinc did not change during these zinc intakes.

The summary of this study was published as an abstract: Spencer, H., Osis, D., Wiatrowski, E., and Coffey, J. Certain aspects of zinc metabolism in man. The Physiologist, 17:334, 1974 (ENCLOSURE 2).

c. Intake, excretion, and retention of zinc in man

These studies were primarily concerned with defining the amount of zinc needed by adults to achieve either zinc equilibrium or a positive zinc balance and with changes in zinc metabolism on zinc supplementation. As mentioned above, zinc equilibrium could be achieved on a dietary zinc intake of 12.5 mg zinc per day. However, an intake of 15 mg/day was found preferable since a larger number of subjects was either in equilibrium or in positive balance on this intake than on the lower intake. Indeed, the Food and Nutrition Board of the National Academy of Sciences has adopted this intake as the Recommended Dietary Allowance (RDA) for zinc for adults. Increasing the zinc intake 10-fold, i.e., from 15 mg to 150 mg per day, by supplementing the constant diet with zinc sulfate tablets, resulted in a doubling of the plasma levels of zinc and in an increase of the urinary zinc from 0.5 mg/day to a level of approximately 3.5 to 4.5 mg/day. Weight reduction induced by using a low calorie diet resulted in a similar excessive loss of zinc as that induced by total

starvation and, here again, the marked zinc loss was not associated with a decrease of the plasma levels of zinc.

These data were summarized and published in a book chapter entitled, "Intake, Excretion, and Retention of Zinc in Man". In: Trace Elements in Human Health and Disease. Vol. 1 Zinc and Copper. A. S. Prasad (ed.); Academic Press, Inc. (publ.); New York 1976 pp. 345-361.

2. Studies of zinc metabolism in animals

a. Studies of the site of the intestinal absorption of zinc in the rat: The absorption of ^{65}Zn from isolated in vivo ligated intestinal loops was determined in the rat. The absorption of ^{65}Zn was greatest from the duodenum and was less from the distal portions of the small intestine. Also, the absorptino of zinc was rapid and a maximum of 25% ^{65}Zn was absorbed in 30 minutes. This absorption value was in good agreement with the absorption of ^{65}Zn in the intact rat.

The data were published in a paper entitled, "Zinc Metabolism in the Rat. I. Intestinal absorption of zinc". Journal of Applied Physiology, 34:58-62, 1973 (ENCLOSURE 3).

b. Studies of intestinal secretion of zinc in the rat

In a second study the sites of the secretion of zinc into the intestine with time were studied in the intact rat and in rats with isolated, intestinal sacs following the intravenous injection of ^{65}Zn. ^{65}Zn was secreted promptly into in vivo ligated segments of the intestine, about 10% of the injected ^{65}Zn was secreted within 30 minutes and a maximum of 15.4% after

3-4 hours. The secretion of ^{65}Zn was uniform throughout the entire small intestine which contained about 80% of the total intestinal zinc.

The data were published in a paper entitled, "Zinc Metabolism in the Rat. II. Secretion of zinc into intestine." Journal of Applied Physiology, 34:63-67, 1973 (ENCLOSURE 4).

3. Radiostrontium studies in man

a. ^{90}Sr-calcium interrelationships in man

Extensive studies of the ^{90}Sr-calcium interrelationships which were carried out during different calcium intakes in man have been published in a paper entitled, "Strontium-90 Calcium Interrelationships in Man". Radiation Research, 24:525-533, 1973 (ENCLOSURE 5).

b. Dietary strontium-90 intake in Chicago

Data on the dietary ^{90}Sr intake due to atmospheric nuclear fallout were determined in the Chicago area by two independent diet sampling methods over an 8-year period. These comparative data were summarized and published in a paper entitled, "Dietary Strontium-90 Intake in Chicago". Health Physics, 25:445-448, 1973 (ENCLOSURE 6).

c. Comparative passage of calcium and strontium across the intestine in man

Studies on the comparative transport of calcium and strontium in both directions across the intestine have been carried out in man. The discrimination ratio of the intestinal absorption of radioactive Ca/Sr was 2.6

during a low calcium intake and was reduced to 1.3 by the addition of calcium to the diet. When the passage of strontium and calcium in the opposite direction was determined, i.e., from the vascular space into the intestine, there was little discrimination against the passage of strontium, the average $^{85}Sr/^{47}Ca$ discrimination ratio of the intestinal excretions being only 1.2. Factors which altered the Ca/Sr absorption ratio were the addition of calcium and the oral intake of radioactive strontium in the absence of food. Both reduced this ratio markedly.

These studies have been published in a paper entitled, "Passage of Calcium and Strontium Across the Intestine in Man". Clinical Orthopaedics, 91:225-234, 1973 (ENCLOSURE 7).

d. Effect of phosphate on the ^{90}Sr balance

Previous studies carried out in this Research Unit have shown that phosphate decreases the intestinal absorption of ^{85}Sr in man. The effect of phosphate on the absorption of ^{90}Sr which is chronically ingested with the food was subsequently studied. As the combined use of phosphate and calcium may be more effective than phosphate alone, the studies were carried out during a high calcium-high phosphorus intake and the results were compared to those obtained during a low calcium-high phosphorus intake. The high calcium intake of 2000 mg/day was due to the addition of calcium gluconate tablets to the constant low calcium diet and the high phosphorus intake of 2000 mg/day was due to the addition of glycerophosphate to the constant diet. The ^{90}Sr and calcium analyses of the diet, urine, and stool were carried out throughout the studies. Table 27 shows that in the control study, during a low calcium intake of

200 mg/day, a phosphorus intake of 800 mg/day, and a dietary ^{90}Sr intake of about 5 pCi/day the ^{90}Sr balance averaged +0.2 ± 0.5 pCi/day. Raising the phosphorus intake to 2000 mg/day during the low calcium intake had little effect on the ^{90}Sr balance which changed from +0.2 ± 0.5 to -0.1 ± 0.5 pCi/day. Table 28 shows that during a high calcium intake of 2000 mg/day and a low phosphorus intake of 800 mg/day the ^{90}Sr balance averaged -0.7 ± 0.4 pCi/day. Increasing the phosphorus intake to 2000 mg/day during this high calcium intake resulted in further negativity of ^{90}Sr balance which averaged -1.3 ± 0.2 pCi/day. These studies have shown that the addition of phosphorus to a low calcium intake of 200 mg/day did not affect the ^{90}Sr balance, while the addition of phosphorus to a high calcium intake resulted in a negative ^{90}Sr balance. Further analysis of the data has shown that the increase in fecal ^{90}Sr and therefore the decrease in ^{90}Sr absorption correlated with the fecal phosphorus content but not with the fecal calcium content.

This material has been summarized and a publication entitled, "Effect of Phosphorus on the ^{90}Sr Balance in Man", is in press in Health Physics.

e. Comparative excretions of strontium isotopes in man

Results obtained in metabolic studies of stable strontium and of ^{90}Sr, which were naturally contained in the diet, and the excretions and retention of ^{85}Sr following oral or intravenous administration of tracer doses of ^{85}Sr were compared in groups of adult males who were studied under strictly controlled dietary conditions. This comparison has shown good agreement between the results obtained with stable strontium, ^{90}Sr, and ^{85}Sr. The net absorption

of stable strontium, of ^{90}Sr, and of ^{85}Sr averaged 12%, 16%, and 20%, respectively. The urinary excretions expressed as percent of the intake averaged 17% and 13% for stable strontium and for ^{90}Sr, respectively, and was lower following the acute administration of ^{85}Sr. There was a good correlation between the urinary excretion of calcium and of each of the three strontium isotopes. In general, very low levels of the urinary calcium were associated with very low levels of urinary ^{90}Sr, ^{85}Sr, and of stable strontium and vice versa, high excretions of calcium were associated with relatively high excretions of these isotopes. The fecal excretions of the three isotopes were rather high and were similar for stable strontium, ^{90}Sr, and ^{85}Sr, the average values ranging from 81% to 88% in the three studies.

This material has been summarized and a publication entitled, "Comparative Excretions of Strontium Isotopes in Man", is in press in Health Physics.

f. Stable strontium balances in man

The effect of orally and intravenously administered stable strontium in man on the retention and excretion of stable strontium was studied. Stable strontium balances were determined in man under strictly controlled dietary conditions in control studies and during both oral and intravenous administration of stable strontium. The diet contained about 1 mg strontium per day and most of this, 88%, was excreted in stool. During the oral intake of 1536 mg strontium per day, given as the lactate, the urinary and the fecal strontium excretions increased markedly and the balance became strongly positive. During the 6-day periods of intravenous infusions of stable

strontium as the gluconate, 30-40% of the infused amount was excreted in the urine and 5-10% in stool. A high percentage of the strontium retained during both oral and intravenous administration was excreted in 30 days after the discontinuation of the strontium administration and there was no evidence of long term retention.

These studies were published, "Metabolic Balances of Strontium in Man". Clinical Orthopaedics, 117:307-320, 1976. (ENCLOSURE 8)

g. Effect of single dietary items on the intestinal absorption of ^{85}Sr in man

Previous studies carried out in this Research Unit have shown that the intestinal absorption of ^{85}Sr was increased by a factor of 2 to 3 when the ^{85}Sr was given without food as compared to the absorption of ^{85}Sr when given with breakfast. An example of these results is shown in Fig. 1. In order to determine which of the food items contained in the breakfast meal contribute to the decrease in radiostrontium absorption the effect of certain single dietary items contained in the breakfast meal were tested. As a first step, the effect of the amount of calcium (45 mg) and of phosphorus (120 mg) contained in the breakfast meal on ^{85}Sr absorption was determined. This small amount of calcium or of phosphorus, given with the oral dose of ^{85}Sr without any food intake, decreased the absorption of ^{85}Sr to the same extent as the entire breakfast meal (Figs. 2 and 3). Twice these amounts of calcium or phosphorus had about the same effect as the smaller amounts. As ^{90}Sr due to nuclear fallout would be ingested with food, the effect of a single dose of calcium and of a single dose of phosphorus on the absorption

of radiostrontium, given with food, was then investigated. A single relatively large dose of calcium (500 or 1000 mg) and of a single relatively large dose of phosphorus (1000 mg) was given with the oral dose of ^{85}Sr during food intake. The single dose of calcium decreased the absorption of ^{85}Sr, the decrease ranging from 40% to 60%. An example is shown in Fig. 4. A smaller amount of a single dose of calcium, 500 mg, was as effective as 1000 mg calcium. The single large dose of phosphate, given with food, had a variable effect. Fig. 5 shows that a single dose of phosphate, given with food, had a slight effect in one case and no effect in the other, while Fig. 6 shows a very marked effect of phosphate on decreasing the absorption of ^{85}Sr and was reproducible in two separate studies. On the average, a single dose of phosphate decreased the absorption of ^{85}Sr by about 30%. The combined use of a large dose of both calcium and of phosphorus, given with food, decreased the absorption of ^{85}Sr more than the single dose of calcium alone (Fig. 7).

These observations indicate that a single relatively large dose of calcium decreases the absorption of radiostrontium ingested with food and that the combined use of a single large dose of calcium and of phosphorus is more effective than either of the two compounds used alone.

These data were presented at the 21st Annual Meeting of the Radiation Research Society in St. Louis, Missouri, May 1973 (ENCLOSURE 9).

h. Factors influencing the intestinal absorption of radiostrontium in man

A summary of various conditions affecting the intestinal absorption of radiostrontium in man has been presented. It was shown that the daily intake

of relatively large amounts of calcium, given in divided doses with food, had little effect on the absorption of ^{85}Sr and the daily intake of phosphate, given in the same manner, decreased the absorption of ^{85}Sr by 20-25%. In contrast, a single relatively large dose of 0.5 to 1 gm calcium or a single dose of 1.2 gm phosphate, given either with or without food, decreased distinctly the absorption of ^{85}Sr and the effect was greater when these amounts of calcium or phosphorus were given in the absence of food. Aluminum phosphate gel was most effective in decreasing the absorption of ^{85}Sr, by an average of 87%, while aluminum alone, given as $Al(OH)_3$, was about 50% as effective as aluminum phosphate gel. Orally administered stable strontium decreased markedly the total body retention of ^{85}Sr but this decrease was not due to a decrease of the intestinal absorption of ^{85}Sr but to an increase of the urinary ^{85}Sr excretion.

The results of these studies were presented at the 5th International Congress of Radiation Research in Seattle, July 1974.

i. Effect of hormones and of the hormonal status on radiostrontium metabolism in man

The effect of certain hormones and of the hormonal status on the intestinal absorption and excretion of radiostrontium has been investigated in man. The functional state of the thyroid gland markedly affected radiostrontium absorption. In a state of increased thyroid function, in hyperthyroidism, the intestinal absorption of ^{85}Sr was in the low normal range and it increased markedly after the correction of the hyperthyroid state as shown by the marked increase of the ^{85}Sr plasma levels and by the decrease

of the fecal ^{85}Sr excretions (Figs. 8-10). Similar results were obtained in a hypermetabolic state which was due to the administration of thyroid extract and following its discontinuation.

In another state of endocrine dysfunction, in hypoparathyroidism, the intestinal absorption of ^{85}Sr was very low and the administration of 200 Units of parathyroid extract (PTE), given daily for 42 days, did not change the absorption of ^{85}Sr from the intestine (Fig. 11). However, changes in ^{85}Sr metabolism were noted in patients with hyperparathyroidism and following the correction of this abnormal state of parathyroid function. Fig. 12 shows that the urinary ^{85}Sr excretions differed markedly in these states of parathyroid function. The urinary ^{85}Sr excretion was high, 20% of the dose, following the intravenous administration of ^{85}Sr in the hyperparathyroid state and these excretions decreased sharply at different time intervals in the post-operative phase. These excretions were lowest, 2%, in the first post-operative month and increased gradually in a 12-month period. The changes in ^{85}Sr excretion were associated with corresponding changes of the urinary calcium excretion (Fig. 12).

Corticosteroids mainly increased the urinary ^{85}Sr excretion when the urinary calcium increased and the intestinal absorption of ^{85}Sr was only somewhat lower than in the control study.

Estrogens decreased the urinary excretion of both ^{85}Sr and of calcium, while androgens had a variable effect but neither of these hormones affected the intestinal absorption of ^{85}Sr (Fig. 13).

These data have been presented at the Annual Meeting of the Radiation Research Society in Miami Beach, May 1975. Radiation Research, 62:578, 1975.

4. Radiostrontium studies in animals

The secretion of ^{85}Sr and ^{47}Ca from the vascular space into the intestine was determined in rats as a function of time during both feeding and fasting. Between 4 and 24 hours the excretion of both isotopes via the intestine increased but the increase in ^{85}Sr excretion was greater than that of ^{47}Ca, the values being 11% and 8.6% of the dose at 24 hours, respectively. Fasting decreased the secretion of both isotopes into the intestine at all time intervals and this effect was more marked for ^{47}Ca than for ^{85}Sr. The $^{85}Sr/^{47}Ca$ ratio of the intestinal excretions was 2.0 during fasting and 1.3 during feeding.

The data of this study was published in the paper, "Passage of ^{85}Sr and ^{47}Ca into the Gastrointestinal Tract in Rats During Feeding and Fasting". Radiation Research, 56:110-121, 1973 (ENCLOSURE 10).

5. Calcium kinetic studies in man

A study was performed in man to determine the rate of exit of calcium from the plasma compartment and its reentry utilizing the integro-differential equation method of tracer analysis. The studies have shown that both the rate of exit of calcium from plasma as its return are extremely rapid. The analysis indicates that most of the calcium which exits from the vascular system returns within 30 min. The external exchangeable calcium volume has been calculated as a function of time. The 30-min. exchangeable volume is approximately three times that of the plasma calcium compartment. All rates and volumes were significantly increased in a patient with Paget's disease of the bone.

These data were published in a paper entitled, "Vascular and Extravascular Calcium Interchange in Man Determined with Radioactive Calcium". Radiation Research, 67:149-161, 1976 (ENCLOSURE 11).

D. Studies of Other Trace Elements

1. Intake, excretions, and retention of ^{210}Po and ^{210}Pb

A collaborative study was carried out with the Radiological and Environmental Research Division of Argonne National Laboratory on the metabolism of naturally occurring ^{210}Po and ^{210}Pb in man. Metabolic balances of ^{210}Po and ^{210}Pb were determined under strictly controlled dietary conditions in adult males. The intakes of the two nuclides were due to the dietary content of these radioisotopes, inhalation from the atmosphere, and smoking of cigarettes. No additional radioisotope was given. The mean dietary intake of ^{210}Pb was 1.25 pCi/day and of ^{210}Po, 1.63 pCi/day. The major pathway of excretion of both nuclides was via the gastrointestinal tract and the urinary excretion was very low. The total excretions of ^{210}Pb and ^{210}Po were greater than the dietary intake and the overall balances were -0.28 and -0.16 pCi/day for the two nuclides, respectively, during a low calcium intake. The ^{210}Pb balances did not change significantly when the calcium intake was increased 7- to 10-fold, while the ^{210}Po balance was more negative during the higher calcium intakes.

The data obtained in this study were published in a paper entitled, "Metabolic Balances of ^{210}Pb and ^{210}Po at Natural Levels". Radiation Research, 69:166-184, 1977 (ENCLOSURE 12).

2. ^{226}Ra studies in man

Balance studies were carried out in man on the intake and excretions of naturally occurring radium-226. During a low calcium intake of an average of 243 mg/day the urinary ^{226}Ra excretion was low and averaged 0.016 pCi/day. Increasing the calcium intake to about 1300 or 2600 mg per day, given as calcium gluconate, did not change the urinary ^{226}Ra excretion, while this excretion was considerably higher when calcium was given as milk. There was no correlation between the urinary excretion of ^{226}Ra and of calcium in any of the studies. The major pathway of ^{226}Ra excretion was via the intestine and the ^{226}Ra balances were in equilibrium under all study conditions.

The data obtained in this study have been published in a paper entitled, "Intake and Excretion Patterns of Naturally Occurring Radium-226 in Humans". Radiation Research, 56:354-369, 1973 (ENCLOSURE 13).

3. Tissue distribution of molybdenum-99 with time in mice

Recent studies indicate that molybdenum is present in water[1] and milk[2] as an environmental pollutant in increasing levels. In the study carried out in this laboratory the tissue distribution of ^{99}Mo was determined in mice with time. The liver, kidney, and pancreas had the highest concentrations of ^{99}Mo both at 1 and 24 hours. At 24 hours ^{99}Mo in the liver remained un-

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1. Kopp, J. F. and Kroner, R. G. Trace metals in waters of the United States Federal Water Pollution Control Administration, Division of Pollution Serveillance, Cincinnati, Ohio (Oct. 1, 1962 - Sept. 30, 1967).

2. Chappell, W. R. An interim progress report for an exploratory and planning phase of an interdisciplinary study of transport and biological effects of molybdenum in the environment, National Science Foundation (1972).

changed, while the ^{99}Mo concentration in most other tissues was lower than at 1 hour. The excretion of ^{99}Mo via the kidney was high, about 36% of the dose, in 24 hours.

These data have been published in the paper, "The distribution and excretion of molybdenum-99 in mice". Health Physics, 25:173-175, 1973 (ENCLOSURE 14).

4. Studies of electrophoretic binding of radioactive rare earths

An in vitro study has been carried out on the binding of the radioactive rare earths ^{140}La, ^{91}Y, ^{153}Sa, and ^{46}Sc to protein components of human serum and of mouse serum utilizing paper electrophoresis and radioassays. ^{140}La migrated with the γ-globulin, ^{153}Sa with all globulin fractions, ^{46}Sc with the β-globulin, while ^{91}Y did not migrate with any of the protein fractions.

A manuscript entitled, "Studies of electrophoretic binding of radioactive rare earths", was published. Health Physics, 28:611-612, 1975 (ENCLOSURE 15).

5. Effect of carrier and of the metal/chelate molar ratio on the metabolism of radioactive yttrium

A study of the effect of varying yttrium chelate molar ratios and of the effect of the yttrium carrier on the tissue uptake of radioyttrium was carried out in mice. Yttrium was given intravenously in chelated form as the strong chelates Y-DTPA, Y-EDTA, Y-CDTA, and as the weak chelates Y-NTA, Y-HEEDTA, and Y-HEIDA. The metal chelate molar ratios were 1:1.2 and 1:5 and the yttrium carrier was either 0.03 mg or 0.001 mg. The tissue distribution and urinary excretion of the yttrium chelates depended on the stability constants at both

metal chelate molar ratios. However, marked differences in the excretion and tissue distribution were noted when yttrium chelates of intermediate or low stability were used at either of the two molar ratios.

These studies were presented at the Fifteenth Annual Hanford Life Sciences Symposium, Richland, Washington, in September 1975 and a paper, "Effect of carrier and of the metal/chelate molar ratio on the metabolism of radioactive yttrium", was published in Biological Implications of Metals in the Environment. Technical Information Center, Energy Research and Development Administration (publ.); 1977 pp. 547-559 (ENCLOSURE 16).

III. PLANS FOR FUTURE STUDIES AND PROPOSED WORK

It is planned to continue the trace element metabolism studies of cadmium, copper, lead, zinc, manganese, and nickel in man. In addition to these investigations, studies of selenium metabolism will be carried out in man. All studies will be carried out under strictly controlled and constant dietary conditions in adult males who will be observed in the Metabolic Research Ward.

A. The Trace Element Studies of the metabolism of cadmium, copper, zinc, lead, manganese, and nickel in man will be carried out as follows.

Metabolic balances of these trace elements will be determined in man under the following study conditions:

a) in control studies during a low calcium intake;

b) during the addition of calcium;

c) during the addition of phosphorus;

d) during the addition of both calcium and phosphorus;

e) during the intake of added zinc.

Lead balances will also be determined during the addition of calcium, given in two different forms, namely, as calcium gluconate tablets and as milk, and during the intake of different levels of dietary protein.

B. Selenium Balance Studies in man will be carried out by determining the analyzed dietary intake of selenium and the selenium excretions in urine and stool

a) in control studies, and

b) during the intake of added zinc.

Methods to be used

1. Cadmium

a) Cadmium balances will be determined during a constant dietary intake in the Metabolic Research Ward. The constant diet will have a calcium content of 200 mg/day and a phosphorus content of 800 mg/day. These balances will be determined by analyzing the dietary cadmium intake and the urinary and fecal cadmium excretions. Representative aliquots of the diet will be analyzed for cadmium in each 6-day metabolic study period as well as aliquots of each 6-day collection of urine and stool. The cadmium balances will be determined for several weeks. Cadmium will be analyzed by atomic absorption spectroscopy.

b) Following the completion of these control studies, carried out during a low calcium intake, the effect of a high calcium intake of 2000 mg/day on the cadmium balance will be studied for several weeks. The high calcium intake will be achieved by adding calcium gluconate tablets to the constant metabolic diet, all other dietary constituents remaining unchanged.

c & d) As the metabolism of calcium may be affected by the amounts of phosphate in the diet, cadmium balance studies will be carried out during the addition of phosphate as well as during the addition of both calcium and phosphate to the constant diet. The phosphorus intake will be increased from 800 mg/day in the control study to 2000 mg/day in the experimental study by adding glycerophosphate to the constant diet. When the effect of a high calcium and of a high phosphorus intake on the cadmium balance will be studied

the calcium intake will be increased to 2000 mg/day and the phosphorus intake will also be increased to 2000 mg/day.

e) The effect of zinc on the cadmium balance will be studied by determining cadmium balances during supplementation of the constant diet with added zinc given as zinc sulfate tablets which will increase the zinc intake to 150 mg/day compared to a dietary zinc intake of 14-15 mg/day in the control study. The cadmium balances will be determined for several weeks during both intake levels of zinc. These studies will be carried out during a normal calcium intake of 800 mg/day and during a phosphorus intake of 800 mg/day. Should the added zinc result in significant changes of the cadmium balances the effect of smaller amounts of zinc, i.e., of 75 mg and of 38 mg/day, will be studied in order to determine the lowest effective dose.

2. Copper

Metabolic balances of copper will be determined for several weeks under strictly controlled dietary conditions during a low and high calcium intake. In the low calcium control studies the calcium intake will be 200 mg/day and the phosphorus intake will be 800 mg/day. The copper balances will be determined for several weeks by analyzing representative aliquots of the diet in each 6-day metabolic period and by analyzing aliquots of each 6-day collection of urine and stool. Copper will be analyzed by atomic absorption spectroscopy.

In the experimental studies of the effect of calcium on copper metabolism, balances of copper will be determined during a high calcium intake of 2000 mg/day in the same manner as during the low calcium intake. The high calcium intake

of 2000 mg/day will be due to the addition of calcium gluconate tablets to the constant low calcium intake of 200 mg/day.

As phosphate may play a role in the copper-calcium interaction, the effect of phosphate alone and the effect of both phosphate and calcium on the copper balance will be studied. Phosphate will be added as glycerophosphate to the constant diet thereby raising the phosphorus intake from a basal intake of 800 mg/day to an intake of 2000 mg/day. In studies of the effect of both a high calcium and a high phosphorus intake on copper metabolism, the calcium intake will be 2000 mg/day and the phosphorus intake will also be 2000 mg/day.

The results obtained in the studies carried out during the high calcium intake and during the combined use of calcium and phosphorus will be compared with those obtained during the low calcium control study in which the calcium intake will be 200 mg/day and the phosphorus 800 mg/day.

In the study of the copper-zinc interaction, metabolic balances of copper will be determined during supplementation of the diet with zinc, given as zinc sulfate tablets, thereby raising the zinc intake from about 14-15 mg/day in the control study to 150 mg/day in the experimental study. The high zinc intake will be given for several weeks. These copper balance studies will be carried out during a normal calcium intake of 800 mg/day and a phosphorus intake of 800 mg/day. As the effect of zinc on copper metabolism may be altered by calcium and/or phosphorus, copper balances will also be determined during zinc supplementation (150 mg zinc per day) during a high calcium intake of 2000 mg/day, during a high phosphorus intake of 2000 mg/day, and during the simultaneous intake of both a high calcium and a high phosphorus intake.

All copper balance studies will be carried out for several weeks.

Plasma levels of copper will be determined serially during the control and experimental study phases.

3. Zinc

Metabolic balances of zinc will be determined for several weeks in control studies during a constant dietary intake of an average of 14-15 mg zinc per day, a low calcium intake of 200 mg/day, and a phosphorus intake of 800 mg/day. Aliquots of the diet and aliquots of urine and stool collections will be analyzed for zinc by atomic absorption spectroscopy in each 6-day metabolic period. Plasma levels of zinc will be determined serially during this study phase.

Following the completion of these control studies the effect of a high calcium intake of 2000 mg/day on the zinc balance will be determined. The high calcium intake will be achieved by supplementing the diet with calcium as calcium gluconate tablets which will be analyzed for both calcium and zinc. The studies of the high calcium intake on the zinc balance will be carried out for several weeks.

The effect of phosphate on the zinc balance will be studied by determining the zinc balances during the addition of phosphate given as glycerophosphate to the constant low calcium metabolic diet thereby increasing the phosphorus intake from an average of 800 mg/day in the control study to 2000 mg in the high phosphate study. In another study phase of the effect of phosphorus on zinc metabolism, balances of zinc will be determined during both a high phosphorus intake of 2000 mg/day and a high calcium intake of 2000 mg/day. The zinc balances will be determined in each 6-day metabolic study period for several weeks in all study phases.

In order to determine the fate of the excess zinc intake (150 mg/day), i.e., the effect of the added zinc on the excretions and retention of zinc will be studied by determining zinc balances during a zinc intake of 150 mg/day. This higher zinc intake will be due to the addition of zinc sulfate tablets to the constant diet which contains about 14-15 mg zinc per day. The zinc balances will be determined for several weeks during the high zinc intake.

Plasma levels of zinc will be determined serially in all study phases.

4. Lead

Balances of lead will be determined for several weeks during a constant dietary intake having a low calcium content of 200 mg/day and a phosphorus content of 800 mg/day. The lead content of the diet and the urinary and fecal lead excretions will be analyzed by atomic absorption spectroscopy in each 6-day metabolic study period.

In the study of the effect of calcium on lead metabolism, metabolic balances of lead will be determined during a high calcium intake of 2000 mg/day. This high calcium intake will be achieved by adding calcium gluconate tablets to the constant low calcium metabolic diet containing 200 mg calcium per day.

As phosphate may affect the metabolism of lead, metabolic balances of lead will be determined during supplementation of the constant diet with phosphate, given as glycerophosphate. The phosphorus intake will be increased from 800 mg/day in the control studies to 2000 mg in the high phosphate studies. The effect of phosphate on the lead balances will be determined during both a low calcium intake (see above) and during supplementation of the diet with both phosphate and calcium, i.e., during a high calcium intake of 2000 mg/day and a high phosphorus intake of 2000 mg/day.

The effect of the dietary protein intake on the metabolism of lead will be studied by determining lead balances during a normal, a low, and a high protein intake. The normal dietary protein intake will be 1 gm/kg body weight, the low protein intake 0.5 gm/kg, and the high protein intake 2 gm/kg. The different protein intakes will be achieved by increasing the meat intake during the high protein intake and by decreasing it during the low protein intake. The calorie content of the three protein diets will be kept constant as the carbohydrate intake will be decreased during the high protein intake and will be increased during the low protein intake.

5. Manganese and Nickel balances will be determined in each 6-day study period for several weeks alsong with the other trace element analyses during the different study conditions outlined above.

B. Selenium Balance Studies

These studies will be carried out in order to determine the dietary selenium intake and the excretions and retention of selenium in man.

a) Metabolic balances of selenium will be determined for several weeks by analyzing the constant diet and the excreta (urine and stool) for selenium in each 6-day metabolic study period. As in all other trace element balance studies, complete collections of urine and stool will be obtained throughout the studies which will be carried out during a normal calcium intake of 800 mg/day and a phosphorus intake of 800 mg/day.

b) As selenium may interact with the metabolism of other trace elements in the body, selenium balances will be determined during supplementation of the diet with zinc. In these studies the zinc intake will be increased from

14-15 mg/day, contained in the constant diet, to 150 mg/day by adding zinc sulfate tablets to this diet.

Selenium in the diet, urine, and stool will be analyzed by the fluorometric method of Watkinson[1]. Also, selenium analysis will be determined by neutron activation and possibly also by atomic absorption spectroscopy using argonne, nitrogen, or hydrogen instead of acetylene.

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1. Watkinson, J. H. Fluorometric determination of selenium in biological material with 2,3-diaminonaphthalene. Anal. Chem., 38:92, 1966.

IV. SCIENTIFIC SCOPE OF THE PROPOSED INVESTIGATIONS

A. Short Description of Proposed Technical Scope and Research Objectives

Scope: The scope of this investigation is to study in man the intake, the pathways of excretion, and the extent of the excretions of several trace metals which have been introduced into the air and water and have entered the food chain. The metabolism of the pollutants scandium, lead, copper, manganese, zinc, and nickel will be studied in man. As selenium is also released into the environment, the study of the metabolism of this trace element in man will be included in the projected program.

Research Objectives: The goal of these studies is to obtain information on trace element metabolism in man, primarily of cadmium, copper, zinc, and lead, by determining balances of these elements under strictly controlled conditions. It is hoped to gain a better understanding of the handling of these trace elements by the human body and of the effect of compounds which may inhibit the intestinal absorption of these elements and/or promote their excretion thereby diminishing their deposition in target organs.

Another objective of the proposed studies of trace element metabolism is to delineate basic aspects of selenium metabolism in man, such as the pathways of excretion and the retention of selenium in man. Furthermore, the studies will also examine whether an interaction of selenium with other trace elements, particularly with zinc, can be demonstrated in man. The study of selenium metabolism in man becomes of importance as selenium is a contaminant which is released into the environment in the process of coal combustion, it is deposited in soil, enters the human food chain, and may be a potential health hazard. The information available at present on selenium metabolism in man is very fragmentary and the delineation of the basic pattern of selenium metabolism in man is indicated.

B. Detailed Description of Proposed Technical Scope and Research Objectives

As several non-radioactive substances which are present in the atmosphere due to industrial pollution may cause toxic reactions in man, the study of the fate and disposition of these elements in the human body becomes of importance. Although some of the trace elements are essential, such as zinc, copper and manganese, large amounts of these and of other elements, such as cadmium and lead, are hazardous to health. The toxicity of these metals is well recognized as well as the toxicity of large amounts of orally ingested zinc or of inhaled zinc (1-3).

A great deal of information is available on the metabolism of various trace elements in different animal species but very little is known on this subject in man. Data on metabolic balances of zinc, copper, cadmium, and lead in man have been reported (4-6), however, the interpretation of some of these studies is difficult. This is due to the fact that the studies have either been carried out under uncontrolled conditions or they were carried out during controlled conditions for too short a period of time to warrant valid conclusions. Some of the studies were carried out in pathologic conditions which preclude extrapolation of the results to normals. The proposed studies are designed to obtain a better understanding of the disposition of the trace elements cadmium, copper, zinc, and lead which are "naturally" contained in food and water and enter the human body at low levels of intake. These substances are present in the atmosphere as particulate matter and in the drinking water as soluble compounds. As larger amounts of these substances are potentially hazardous, the infor-

mation obtained in the proposed trace element studies in man is relevant to the effect of environmental pollution in human beings. These studies will give information on the amounts of the various trace metals contained in the human diet, the route and the extent of their excretion and the amounts retained in the body.

The studies will also show whether certain normal constituents of the human diet, such as calcium and phosphorus, affect the metabolism of these trace elements. To our knowledge, very little information has been obtained under controlled dietary conditions on the effect of different intake levels of calcium, of phosphorus, or of the combined use of these inorganic elements on the metabolism of cadmium, zinc, or copper, while some information is available on the effect of calcium on the metabolism of lead in man (7). However, one has to consider that the latter studies have been carried out at a time when the present-day methods for analysis of lead were not available. Calcium and phosphorus, given singly or combined, may modify or inhibit the intestinal absorption of several of the trace elements under study and the accumulation of these potentially toxic elements in the body may thereby be minimized or prevented. As the intestinal pH may affect the solubility of the trace elements in the intestinal lumen the absorption of certain trace elements may be altered. This may particularly apply to the intestinal absorption of lead. The type of the diet, i.e., whether it is an alkaline-ash or acid-ash diet, depending on the dietary protein content, may affect the transport of lead across the intestine. The proposed studies, using diets of different protein contents, may clarify some of the problems involved in the availability of certain trace elements for absorption depending on the

composition of the diet. The study of this aspect is of relevance because the entry of potentially hazardous trace elements into the body may be easily changed by modifying the composition of the diet. Information will also be obtained on the interaction of different trace elements in the human body, for instance, on the interaction of cadmium and zinc, of copper and zinc, of copper and calcium, and of lead and calcium. This can be achieved by changing the ratios of the various "pairs" of these elements in the diet by adding either zinc or calcium to the daily dietary intake. Supplementation of the diet with zinc, given as zinc sulfate, will change the dietary cadmium/zinc ratio as well as the copper/zinc ratio. Similarly, the addition of calcium as calcium gluconate to the diet will change the dietary cadmium/calcium, the copper/calcium, and the zinc/calcium ratios.

The functional role of manganese in man is not well understood at present. The proposed manganese balance studies will provide information on the dietary intake of manganese and on the pattern of excretion of this essential trace element and will provide data for comparison with those reported by other investigators.

The studies of nickel metabolism in man will be of interest as nickel has been found in air and in precipitation in water as determined at the Health and Safety Laboratory of the U. S. Energy Research and Development Administration in New York City. There is also a possibility that nickel may enter the food chain as nickel may replace lead as an additive to gasoline and may, thereby, become an atmospheric pollutant from automobile exhaust. The nickel balances determined in this Research Unit are expected to provide information on the dietary content of nickel and on the pathways of excretion of this

element. The availability of data of nickel balances will also offer a basis for comparison of the metabolic behavior of nickel and of lead, i.e., on the comparative pathways of excretion and on the magnitude of excretions of these two trace elements.

As the proposed trace element studies will be carried out under strictly controlled dietary conditions in the Metabolic Research Ward for sufficiently long periods of time the results obtained are expected to provide reliable information on several aspects of the metabolism of these trace elements in man. It is realized that the analyzed dietary intake of the various trace elements under study does not represent the entire intake. Inhalation and subsequent ingestion of atmospheric particulates due to air pollution may contribute an additional, substantial part of the daily intake. Despite this shortcoming of the inability to determine the trace element intake which is due to the inhalation of unknown amounts of these elements, the proposed trace element balance studies carried out under strictly controlled conditions in man are expected to provide a better basis for the understanding of the handling of these elements by the human body and of the processes which may result in toxic effects.

A great deal of information is available on the tissue distribution and metabolism of selenium in animals but very little is known on the subject in man. To our knowledge, no systematic study on the excretion and retention of selenium ingested with the diet has been reported in man. An increase of the selenium content of the human diet may be expected to occur due to the release of selenium into the atmosphere in the process of coal combustion, its deposition in soil, and its entry into the human food chain. The proposed

studies are expected to delineate the dietary intake of selenium, the pathways of excretion, the extent of these excretions, and the retention of this trace element in man, thereby defining the basic pattern of selenium metabolism in man. The selenium balance, carried out during a normal zinc intake and during zinc supplementation, may indicate changes in selenium metabolism as animal studies have shown that selenium interacts with other trace elements in the body. The study of selenium metabolism in man is relevant, not only because selenium is an essential trace element but the excess intake of selenium is potentially hazardous to health and may also induce a trace element imbalance in man.

V. SCIENTIFIC BACKGROUND

The concentration of several non-radioactive substances, such as cadmium, copper, lead, and zinc has increased in the atmosphere in the past 2 to 3 decades due to industrial use of these substances. The inhalation and ingestion of these airborne pollutants are potentially hazardous to health and the deposition of these metals in various tissues in the human body may result in the development of serious disease. Some of the effects of these trace elements are briefly described.

Cadmium: Cadmium has been shown to be toxic to animals and man. In several species of animals a relationship between cadmium and hypertension has been established (8,9). Following subcutaneous injection, large amounts of cadmium were found in the renal cortex (10,11), in the liver, and in the gastrointestinal tract (10). Growth retardation and anemia has also been attributed to cadmium (12). Cadmium has been shown to be carcinogenic and to result in the development of neoplastic lesions (13,14). Interaction between cadmium and other elements has been reported. A cadmium-zinc antagonism has been reported in several animal species (15,16) and cadmium has been shown to decrease the copper and iron content in the liver (16).

Cadmium which enters the body in sufficient amounts either by inhalation or by ingestion may produce toxic changes. The average daily dietary cadmium intake has been estimated to range from 15 to 35 μg (17) and this intake is in part due to the intake of seafoods, grains, and kidneys of animals. The cadmium content of fresh, preserved, and processed foods has been shown to differ (17). It has not been clearly defined how much of the ingested cadmium is absorbed. Conflicting results have been reported on the excretion

and retention of cadmium in man. In one study it has been estimated that on an estimated dietary cadmium intake of 23 µg/day the urinary excretion of cadmium accounts for about 18 µg/day and that 3 µg/day are retained (17). Other studies estimate that 2 µg of the ingested cadmium are absorbed per day (18,19). In addition to the dietary intake of cadmium, a small part of the exposure to cadmium is due to smoking of cigarettes. A substantial fraction of the cadmium contained in cigarette tobacco is contained in the cigarette smoke (20,21). The maximum allowable concentration (M.A.C.) of cadmium has been estimated to be 100 $\mu g/m^3$ air. However, toxic changes may occur in prolonged exposure to lower doses. The particle size, the concentration, and the chemical activity apparently play an important role in causing toxic changes in man. Inhalation of cadmium may lead to the development of chemical pneumonia and of diffuse emphysema (20). Inhaled cadmium passes rapidly from the lung into the circulation and is deposited in the liver and kidney (22).

It has been estimated that the human body contains about 30 mg cadmium and that one-third of this is contained in the kidneys (18). Exposure to high concentrations of cadmium may cause damage of the proximal renal tubules resulting in the development of the acquired Fanconi syndrome. This disease is characterized by glycosuria, phosphaturia, aminoaciduria, severe osteomalacia, and multiple skeletal fractures (23,24). Deposition of cadmium in the kidney has been related to the development of hypertension in animals and man. The increase in blood pressure in man followed inconsistently the exposure pattern to cadmium, although an increase of the blood pressure with advancing age had to be considered (25). The tissue concentration of cadmium has been found to increase with age in patients with different

diseases (26). A relationship between the cadmium and zinc content in the kidney has been postulated and a high cadmium/zinc ratio has been reported to be associated with arterial hypertension and shortened life span in man (19). In a survey the concentration of both cadmium and zinc in plasma were increased in hypertension (25). However, a causal relationship between cadmium exposure and hypertension in man has not been established with certainty (25). Although there is no direct evidence at present that the small amounts of cadmium which are deposited in the kidney due to ingestion of cadmium with the diet or due to inhalation from cigarette smoke (26) are toxic, exposure to increasing amounts of cadmium present in the air and water may constitute a health hazard to man. Recent studies of cadmium metabolism carried out in man in this Research Unit have shown that the dietary cadmium intake averaged 32.4 µg/day, that the fecal cadmium excretion corresponded to 65% of the intake, the urinary cadmium excretion to 48% of the intake and that the cadmium balance was slightly negative. This negativity of the cadmium balance may be due to the fact that the total cadmium intake, which in part is due to inhalation from atmospheric pollutoin, is greater than the analyzed dietary cadmium intake. This greater unaccounted intake would therefore result in a negative balance.

Copper: Most of the information on the effects of excess copper has been obtained in animal studies and severe anemia, internal hemorrhage, cirrhosis of the liver, gastric ulceration, loss of weight, and incoordination have been reported (27,28). In exposure to excess copper, the liver content of copper increases markedly (29).

Copper is an essential trace element. It is found in hemoglobin and in serum (30,31) and appears to be essential for bone mineralization as copper deficiency has been reported to interfere with the mineralization of the skeleton (32). The major organ for copper storage is the liver (30,31) but brain tissue has been reported to contain about the same amount of copper as the liver, while the copper content of the kidney, heart, and spleen are low (31). The human diet has been estimated to contain as much as 5 mg copper per day and 30% of this is believed to be absorbed. Of the absorbed copper, 80% is excreted in bile, 4% in urine, and the rest is re-excreted into the intestine (33). The intestinal absorption of copper has been studied with ^{64}Cu in man (34). The absorption of the tracer was found to be maximal in the first hour and to continue for 3 1/2 hours.

Large amounts of copper which enter the human body can cause severe toxic reactions. For instance, excess copper can lead to the development of jaundice, hemolytic anemia, oliguria, leucocytosis, and abnormal liver functions (35). Penicilliamin is considered to be the treatment of choice for copper intoxication as it increases the urinary copper excretion and decreases the serum copper level. In hepatolenticular degeneration (Wilson's disease) the amounts of copper in the liver and brain are increased (36-38) and chelating agents increase the urinary copper excretion and decrease the tissue content of copper (39). Recent studies of copper metabolism carried out in man in this research unit have shown that on a copper intake of approximately 1000 µg/day practically all the copper was excreted in stool, the urinary copper was very low, about 10 µg/day and the copper balance was in equilibrium or slightly negative, -36 µg/day.

Lead: The concentration of lead has been measured in air (40), in ocean water (41), in the human diet (40), and in human tissues (42). Large amounts of atmospheric lead are derived from motor vehicle exhausts, lead is contained in water due to industrial pollution, and the annual pollution of air with lead is increasing steadily. Although these sources may account for the major portion of the inspired lead the amount of inhaled lead is relatively small compared to the much larger portion of ingested lead which is derived from the soil and contaminates the vegetation. The contamination of soil with lead derives from the atmosphere and water. The increasing exposure to lead may pose a considerable health hazard (43). For instance, high concentrations of lead in blood were found in black children who lived near a battery plant (44). High plasma levels of lead and high urinary excretions of lead are found in areas where the atmospheric lead is high. The high plasma and urine levels are not only due to inhalation of lead but also to absorption from the gastrointestinal tract (45).

The lead content of the human diet has been reported to vary by a factor of 10 and amounts ranging from 70 to about 700 µg per day have been cited. The total excretions of lead in stool and urine were reported to be high (46). The absorption of ^{212}Pb in humans has been reported to vary from 1.3 to 16.0% and younger persons appear to absorb greater amounts than older persons (47). Lead accumulates in the red blood cells and may be released from these cells when the red blood cell dies (47). The many aspects of the disposition of lead in the human body and of lead toxicity have been described in a recent review (48).

Several brands of American cigarettes have been shown to contain lead, cadmium, and zinc (49). The cigarette smoke contains lead (49). Other investigators have also made measurements of lead and cadmium in cigarettes and in cigarette smoke (22,50). Smoking 2 packages of cigarettes contributes about 20% of lead, 20% of cadmium, and less than 1% of zinc to the daily intake of these metals (49).

The concentration of lead in blood and the excretion of lead in urine of persons not occupationally exposed to lead have been reported to be about 27 µg% per day and 35 µg per liter, respectively (51). The blood levels of lead and the urinary excretions of lead were found to be higher in males than in females in a survey carried out in Italy (51). Tissue distribution studies in man have shown that bone contains about 90% of the total lead body burden and that the concentration of lead in soft tissues increases with age (43,52). The patholgic changes induced by chronic lead poisoning are well known and the first case of lead poisoning in the United States was described more than 60 years ago (53). Numerous reports of lead poisoning have been published since that time, particularly in children. Chronic, subacute or acute lead poisoning is associated with anemia, with inhibition of heme synthesis and with increased urinary excretion of ALA (amino levulinic acid). The excretion of ALA was also found to be increased in 50% of persons occupationally exposed to lead (54,55). Brain damage (56,57) and many cases of lead encephalopathy have been reported. Persons exposed industrially to lead accumulate considerable amounts of lead in brain and in the kidney and renal tubular damage associated with aminoaciduria (58) as well as hypophosphatemia and rickets have been reported in children (59). The survival time of red blood cells is shortened in lead poisoning and in persons heavily exposed to lead although

these persons may be free of clinical symptoms (60). The use of chelating agents for the treatment of lead poisoning has been reported in the past 25 years (61-64). A lead-calcium interrelationship has been reported by Aub many years ago (7). A recent study reported that decreasing the dietary calcium intake in rats resulted in increased intestinal absorption of lead, in increased blood levels, and in increased body burden of lead (65).

Lead balance studies carried out in man in this Research Unit showed that the dietary lead intake was approximately 250 µg/day and that the urinary and fecal lead excretions varied a great deal. Balance studies of ^{210}Pb carried out in man have shown that the fecal ^{210}Pb accounted for most of the ^{210}Pb intake, the urinary ^{210}Pb was low and the ^{210}Pb balance was slightly negative (66).

Zinc: Great emphasis has been placed on the importance of zinc in the human diet in the past decade. Zinc is an essential trace element and is an essential metalloenzyme and/or cofactor. However, the inhalation or the ingestion of excess amounts of zinc can be toxic (1-3). Zinc has been reported to be a growth factor and has been shown to be essential for sexual maturation and to promote wound healing (67-69). Zinc is bound loosely as well as firmly to different proteins (70) and is specifically bound to α_2-macroglobulin. Zinc has been shown to be essential for DNA synthesis (71) and to be a constituent of the RNA molecule. Abnormal amounts of other trace elements in the body, such as cadmium, copper, and also of calcium, may interfere with the normal biological function of trace amounts of zinc in the body. This trace element imbalance may lead to the development of disease states. For instance, excess amounts of cadmium in organs which

have high concentrations of zinc, such as the prostate gland or the testes, have been shown to result in pathological changes in these organs, most likely as a result of a selective zinc deficiency in these organs (72,73). In fact, studies in rats have shown that excess cadmium does result in local zinc deficiency of these tissues (74). Calcium has also been shown to antagonize the biological effects of zinc in animals and to result in severe skin changes, such as parakeratosis and in severe malnutrition and death. The calcium-zinc antagonism in animals has been shown to be the result of the presence of excess phytic acid in the diet (75). With regard to the interaction between copper and zinc, it has been demonstrated that copper interferes with the intestinal absorption of ^{65}Zn in rats (76). An extensive review of the biological functions of zinc has been published several years ago (77). The intestinal absorption of ^{65}Zn has been determined in different mammalian species (78) and the effect of stable zinc on the absorption of ^{65}Zn has been reported (79). Zinc has been shown to facilitate wound healing in general (80) and to promote the reversal of lesions which are due to peripheral vascular disease (81). Extensive investigations of zinc metabolism in man have been carried out by this group using ^{65}Zn as the tracer. Following the intravenous administration of ^{65}Zn the urinary excretion was very low, while the fecal ^{65}Zn was high, the fecal/urinary ^{65}Zn ratio being approximately 20:1 (82). The biological half-life, the long term turnover of ^{65}Zn, and the ^{65}Zn retention were determined by total body counting. The intestinal absorption of zinc was determined using orally administered tracer doses of ^{65}Zn (83). The absorption of ^{65}Zn was found to be variable and was shown to depend on the

nutritional status of the subject. The influence of certain factors, such as calcium, on the absorption of ^{65}Zn has been investigated (84), however, analysis of stable zinc to determine zinc balances were not performed simultaneously because of the unavailability of the atomic absorption spectrophotometer at that time.

The excretion of trace amounts of the zinc chelates $^{65}ZnEDTA$ and $^{65}ZnDTPA$ has been studied in man (85) and the effect of carrier amounts of the two chelating agents (EDTA and DTPA) which have a high stability constant for zinc on the removal of ^{65}Zn from the human body was investigated (86). Both EDTA and DTPA were found to be effective in enhancing the ^{65}Zn excretion but DTPA was more effective than EDTA in the removal of ^{65}Zn. Subsequently, studies of stable zinc in man have been carried out under controlled dietary conditions by this group. These studies have delineated the amounts of dietary zinc needed to achieve zinc equilibrium or a positive zinc balance in adults. Zinc equilibrium can usually be achieved on a dietary intake of 12.5 mg zinc per day, however, a zinc intake of 15 mg/day resulted in equilibrium in a larger percentage of the subjects studied than the lower intake (87,88). The studies have also shown that weight loss, induced either by calorie restriction or by total starvation in obese persons, results in excessive losses of zinc. These high zinc excretions were not associated with a decrease of the plasma levels of zinc, indicating that these levels are not reliable indicators of the zinc status during conditions of weight loss.

Manganese: Manganese is an essential trace element. The requirement for maximum growth for children has been estimated to range from 0.2-0.3 mg/kg body weight (89). The average daily dietary intake of manganese has been estimated to range from 2 to 5 mg or from 10-25% of the total body pool of 20 mg (89). The mechanism of the intestinal absorption and of the transport of manganese have been extensively studied (90). Metabolic balances of manganese have been determined in humans. The excretion patterns and retention of manganese have been studied in college-age women (91,92). Although there is no definitive evidence for a manganese homeostasis there is an apparent homeostatic mechanism as the blood levels of manganese and the tissue concentrations of manganese remain relatively constant (89) regardless of the manganese intake. This constancy is apparently due to a compensatory increase in the rate of manganese excretion (93). Disorders of manganese deficiency or of excess manganese appear to be caused by factors which would influence the rate of turnover of the body pool of manganese (94).

Neurological disorders have been reported in miners who were exposed to manganese dust (95,96). The effect of a high manganese intake affects the utilization of other nutrients and/or metals. A high intake of manganese interferes with the intestinal absorption of iron (97) and iron deficiency was found to predispose to greater absorption of manganese (98). An interaction between manganese and calcium has been reported. Rats receiving a high manganese intake developed negative calcium and phosphorus balances and severe rickets (99). On the other hand, dietary calcium does not interfere with the tissue accumulation of manganese and, in fact, dietary calcium may enhance the absorption of manganese from the intestine (100). Recent manganese balance studies carried out in this Research Unit have shown that on a dietary

manganese intake of 2000 µg/day, the fecal manganese excretion practically accounts for the entire intake, in fact, the fecal manganese excretion in many instances was higher than the intake probably as a result of the unaccounted intake due to inhalation from atmospheric pollution. The urinary manganese excretion was very low, about 10 µg/day, and the manganese balance was either negative or in equilibrium.

Nickel: The average human diet has been reported to contain 300-500 µg nickel per day (101). The dietary content of nickel depends on the composition of the diet as diets comprised mainly of plant materials supply more nickel than those containing primarily foods from animal sources (102). Some foods may be contaminated with nickel during processing. Also, the nickel content may be increased by cooking foods in stainless steel utensils in an acid medium. Nickel was found in some water supplies in a concentration of about 1-30 µg/liter, and air samples yielded about 0.02 µg/m^3 (101). The excretion of nickel appears to depend on the route of administration (103). Orally administered nickel is mainly excreted in feces while intravenously administered nickel is excreted in urine. In rats the excretion of nickel was reported to be 1.6% in urine and 74.4% in feces, regardless of the nickel intake (104). In man the amount of nickel excreted in urine has been reported to be small or even negligible (101) and this excretion has been estimated to correspond to about 5% of the dietary nickel intake (105). The intestinal absorption of nickel is low and very large doses are required to overcome this low absorption (101). Recent studies of nickel metabolism carried out in man in this Research Unit have shown that the dietary nickel

intake ranges from 206 to 295 µg/day and that the urinary nickel excretions were lower during a calcium intake of 1300 mg/day than during a calcium intake of 800 mg/day, the average values being 38 µg vs. 63 µg/day, during the higher and lower calcium intake, respectively. The fecal nickel excretion was simialr during the two calcium intakes. The nickel balance was slightly positive during the two calcium intakes, +84 and +112 µg/day, respectively.

The toxicity of nickel in mammals is low and is comparable to that of chromium, tin, barium, and silver. Nickel in human tissues is deposited in the lung, aorta, trachea, kidney, larynx, liver, and bone in decreasing order (101). Cases of nickel intoxication and diseases due to exposure to nickel have been reported. Respiratory tract neoplasia and nickel dermatitis are quite common among exposed workers in nickel refineries. Nickel has been implicated as a pulmonary carcinogen in tobacco smoke (106). Nickel in the serum has also been reported to be high in patients with myocardial infarction (107).

Selenium is an essential nutrient, however, excess amounts are toxic (108) and animal experiments indicate that a dietary intake of more than 5 µg/gm can be harmful (109). Selenium has a high affinity for sulfur-containing proteins and forms a strong bond with sulfur (110-113). Also, selenium provides protection against cadmium and mercury toxicity (114-116). Excess dietary selenium intake has been reported to aggrevate lead toxicity in rats and resulted in increased lead levels in blood, liver, kidney, and bone (117). Also, the high selenium intake appeared to have contributed to a trace element imbalance as the concentration of zinc and of copper in the liver decreased (117)

and this trace element imbalance may have played a role in exaggerating the toxicity of lead. Interactions of selenium with other trace elements in the rat have been reported (118). Data on the selenium content of the human diet have been published (119-122). In the United States the dietary selenium intake has been reported to range from 60-150 µg/day (120), while in Canada the selenium intake has been estimated to be 197 µg/day (122). The major dietary source of selenium is wheat flour but animal products, such as meat, poultry, and fish, also contribute to this intake. One-half of the human selenium intake is believed to derive from farm animals and one-eighth from poultry products (122). Data on the selenium content of different food items in the United States have been recently reported (123). The selenium content of grains and of livestock depends on the amount of selenium in the soil. The metabolism of selenium has been studied in young women in New Zealand (124). Also, studies have been carried out in young New Zealand women using ^{75}Se as the tracer (125). The intestinal absorption of selenium in the three subjects studied ranged from 44% to 64% of the dose and 14-20% of the absorbed selenium was excreted in urine. ^{75}Se had a longer residence time in muscle and bone than in the liver. Epidemiological studies in children and studies in animals have shown that the incidence of caries is increased by selenium (126). In view of the potentially hazardous effects of excess selenium demonstrated in animals and the reports which indicate release of selenium into the environment in the process of coal combustion (127-129) the proposed studies of selenium metabolism in man are highly relevant.

VI. PUBLICATIONS AND PRESENTATIONS OF PAPERS

A. Publications

1. Zinc metabolism

Methfessel, A. H. and Spencer, H. Zinc metabolism in the rat. I. Intestinal absorption of zinc. J. Appld. Physiol., 34:58-62, 1973.

Methfessel, A. H. and Spencer, H. Zinc metabolism in the rat. II. Secretion of zinc into intestine. J. Appld. Physiol., 34:63-67, 1973.

Methfessel, A. H. and Spencer, H. Intestinal absorption and secretion of ^{65}Zn in the rat. In: Trace Element Metabolism in Animals-2. W. G. Hoekstra, J. W. Suttie, H. E. Ganther, and W. Mertz (eds.); University Park Press (publ.); Baltimore 1974 pp. 541-543.

Spencer, H., Osis, D., Kramer, L., and Wiatrowski, E. Studies of zinc metabolism in normal man and in patients with neoplasia. In: Clinical Applications of Zinc Metabolism. W. J. Pories, W. H. Strain, J. M. Hsu, and R. L. Woosley (eds.); Charles C. Thomas (publ.); Springfield 1974 pp. 101-112.

Spencer, H., Osis, D., Kramer, L., and Norris, C. Intake, excretion, and retention of zinc in man. In: Trace Elements in Human Health and Disease. Vol. 1. A. S. Prasad (ed.); Academic Press, Inc. (publ.); New York 1976 pp. 345-361.

2. Other trace elements

Rosoff, B. and Spencer, H. The distribution and excretion of molybdenum-99 in mice. Health Phys., 25:173-175, 1973.

Spencer, H., Kramer, L., Samachson, J., Fisenne, I., and Harley, N. Intake and excretion patterns of naturally occurring radium-226 in humans. Radiat. Res., 56:354-369, 1973.

Rosoff, B. and Spencer, H. Studies of electrophoretic binding of radioactive rare earths. Health Phys., 28:611-612, 1975.

Rosoff, B. and Spencer, H. Effect of carrier and of the metal/chelate molar ratio on the metabolism of radioactive yttrium. In: Biological Implications of Metals in the Environment. Technical Information Center, Energy Research and Development Administration (publ.); Springfield, VA 1977 pp. 547-559

Spencer, H., Holtzman, R. B., Kramer, L., and Ilcewicz, F. H. Metabolic balances of ^{210}Pb and ^{210}Po at natural levels. Radiat. Res., 69:166-184, 1977.

Spencer, H., Rusin, Sr. M. C., Holtzman, R. B., and Kramer, L. Metabolic balances of cadmium, copper, manganese, and zinc in man. Submitted for publication.

3. Radiostrontium metabolism

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4. Calcium metabolism

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B. Presentations and abstracts

1. Zinc metabolism

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Spencer, H., Osis, D., and Kramer, L. Disposition of excess zinc by the human body. Clin. Res., 24:584, 1976.

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3. Calcium metabolism

Spencer, H., Friedland, J., and Samachson, J. Thyroid function and calcium metabolism in man. J. Nutr., 103:XIX, 1973.

VII. SCIENTIFIC PERSONNEL

a) At the Metabolic Research Unit, Veterans Administration Hospital, Hines, Illinois

Dr. Herta Spencer, Project Director

Dr. Joseph Samachson, Biochemist Consultant

Dr. Nunilo Rubio, Assistant Chief, Metabolic Unit

Dr. Elenita Rubio, Attending Physician

Lawrence Case, Health Physicist

Clemontain Norris, R.N., Head Nurse, Metabolic Unit

Michele DeBartolo, Research Dietitian, Metabolic Unit

Laboratory technicians, staff nurses, practical nurses, nursing assistants, and practical dietitians.

b) At the Environmental Measurements Laboratory, U. S. Department of Energy, New York, New York

Mr. Edward P. Hardy, Jr., Director, Environmental Studies

Mr. Burton Bennett, Physicist

c) At Argonne National Laboratories, Argonne, Illinois

Dr. Richard B. Holtzman, Associate Chemist,

Radiological Physics Division

VIII. A. PROPOSED BUDGET FOR THE CONTRACT PERIOD

April 1, 1978 to March 31, 1979

Salaries and Wages		
Program Director, M.D. (25% of time)	$ 0	
Biochemist, Ph.D. (10% of time)	1,500	
Nurses (2) (70% of time)	22,000	
Technician (1) (80% of time)	7,250	
Secretary (30% of time)	3,000	
Fringe Benefits, 12% of salaries	4,050	
Indirect Costs at 52.3% S&W	17,652	
Total		$55,452
Glassware, Chemicals and Other Consumable Supplies		2,280
Other Miscellaneous (Repairs, Maintenance)		1,100
Travel (2 investigators to attend national scientific meetings)		500
Total		$59,332
Less Contractor's Cont. (5%)		2,967
Commission's Contribution		$56,365
In addition to above: VA contribution		$10,000

Requested budget for 1980 - $59,183

APPROVED: Matthew E. Creighton, S.J., M.D.

REV. MATTHEW E. CREIGHTON, S.J.
Director, Research Services

VIII. B. Justification for the Budget

All individual items in the proposed budget for the Contract period April 1, 1978 through March 31, 1979 are the same as the budget that has been previously requested, even though the salaries of the personnel had been increased twice since the last request and the overall cost of living has increased. The Indirect Cost (Institution Charge) of Loyola University Medical School of 52.3%, i.e., of $ 17,652, and the expenses for the Indirect Cost and for Fringe Benefits ($ 4050) have to be paid from the overall budget and these amounts will be deducted from the budget by Loyola University. Therefore, the available funds will be reduced by $ 21,702, so that only $ 34,663 will be available for carrying out the proposed studies. It should be emphasized that only a minimum amount has been requested in the proposed budget which will enable us to carry out the extensive studies. In order to economize, the time spent by the nurses on this project has been further reduced from 90% to 70% in the current Contract year. This reduction is necessary in view of the current VA salary scale for nurses which had been increased twice sine December 1975 when the previous budget was submitted. The employment of the nurses is essential for carrying on the studies under controlled conditions. Only one, instead of two, technicians (previously 90% time) will be employed and the time spent by the one technician had to be decreased from 90% to 80% and the time spent by the secretary will only be 30% for the same reasons. In view of these circumstances, any reduction of the requested budget would make it extremely difficult to carry out the proposed studies.

IX. STATEMENT OF UNEXPENDED FUNDS

ERDA funds provided for April 1, 1976 through March 31, 1978		$45,800
Unexpended funds from previous period		0
Total ERDA funds available		45,800
Costs from April 1, 1976 through December 31, 1977	$36,200	
Estimate of costs from January 1, 1977 through March 31, 1978	$ 9,600	
Total	$45,800	
UNEXPENDED FUNDS		0

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XI. STATEMENT REGARDING REVIEW OF THE JUDGMENT OF THE PRINCIPAL INVESTIGATOR

Prior review of the judgment of the Principal Investigator is provided by the Committee of Clinical Investigation of the Stritch School of Medicine, Loyola University. In addition, these studies have also been approved by the Human Studies Committee of the VA Hospital, Hines, Illinois.

The procedures used in the studies performed in the Metabolic Ward will be explained to the patients and informed consent will be obtained on the official VA Form #1086 and a special information sheet has been set up entitled, "Statement to the Patient". There is no risk involved in performing the proposed studies which are mainly concerned with the excretion and retention of naturally occurring trace elements cadmium, copper, zinc, lead, manganese, and nickel, which are contained in the diet and the drinking water. The amounts of supplemental zinc will be given in a dosage which is considerably less than that recommended for therapeutic purposes. This group has extensive experience in using supplemental zinc. The dose of the added zinc which will be used in these studies is well tolerated and does not cause any untoward reactions.

FIGURE 1

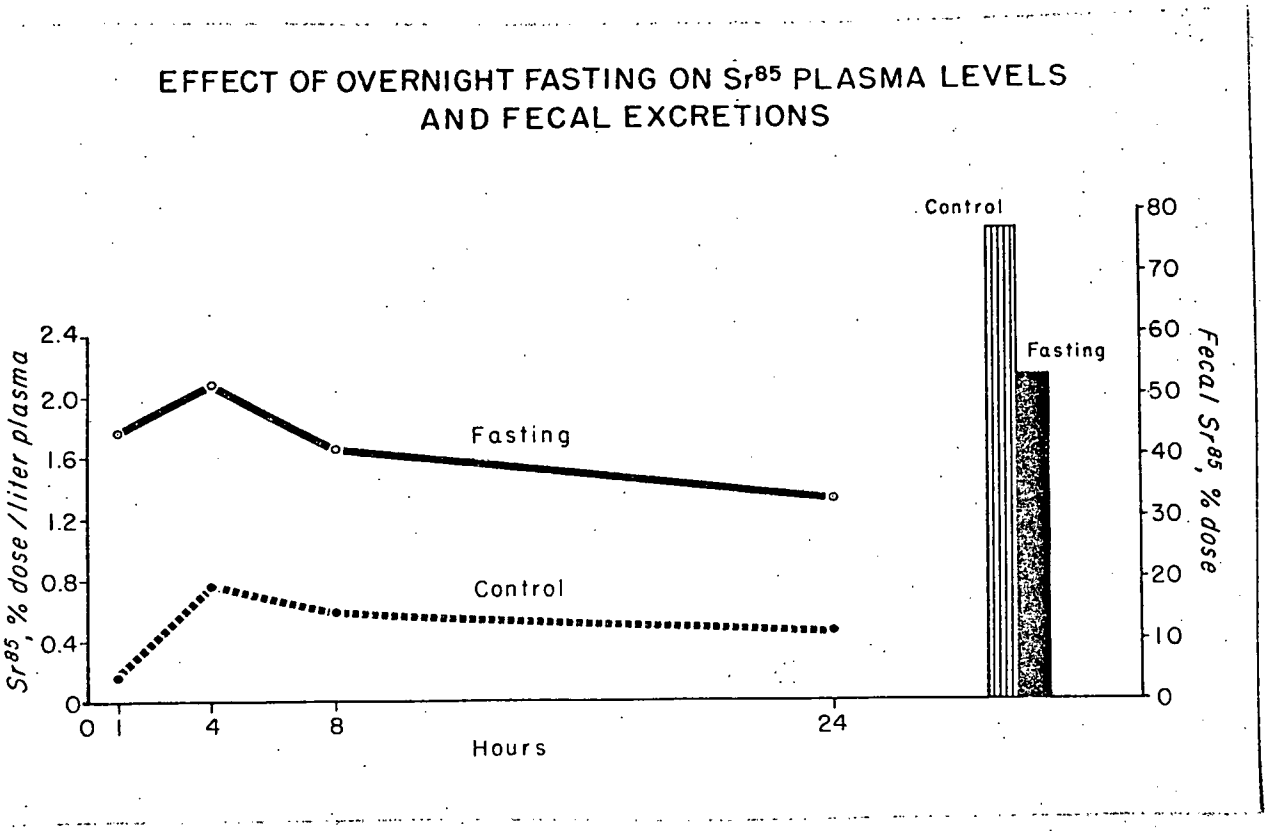


FIGURE 2

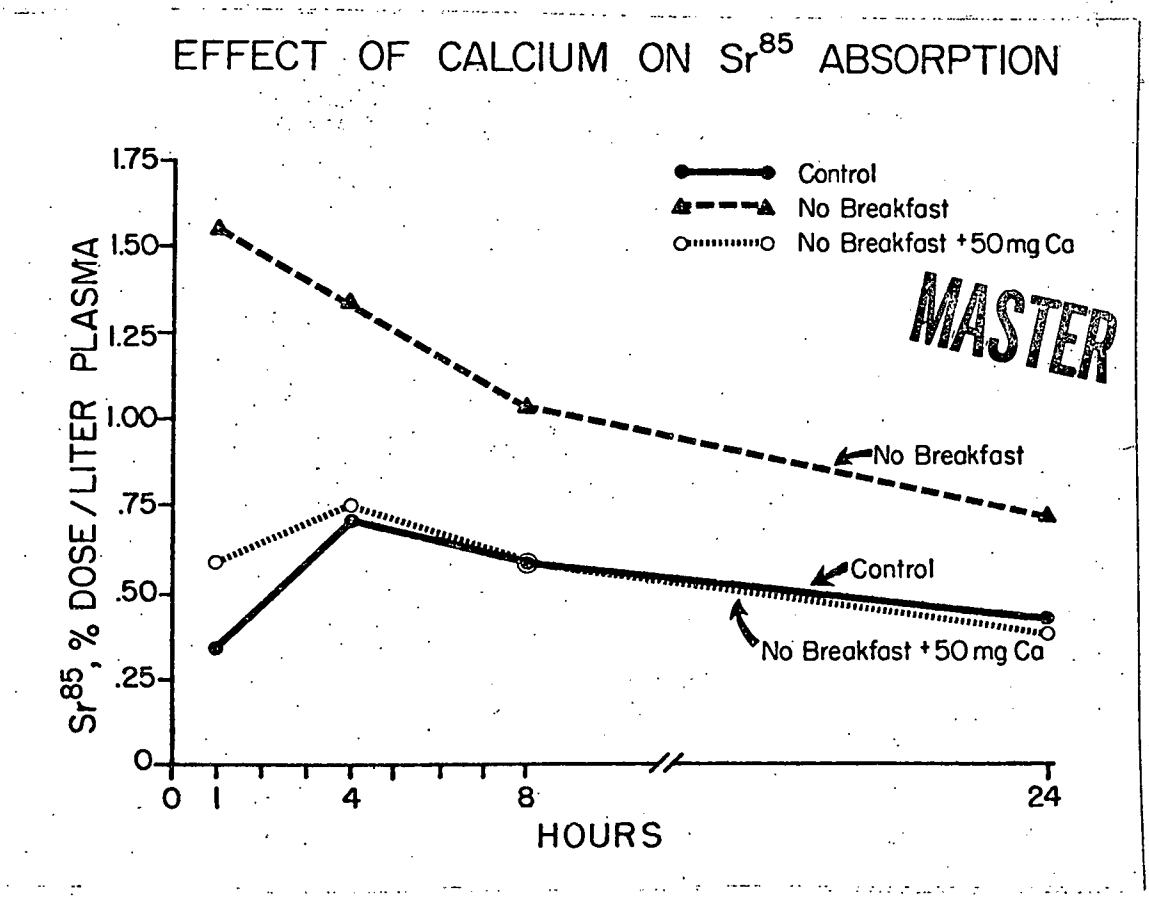
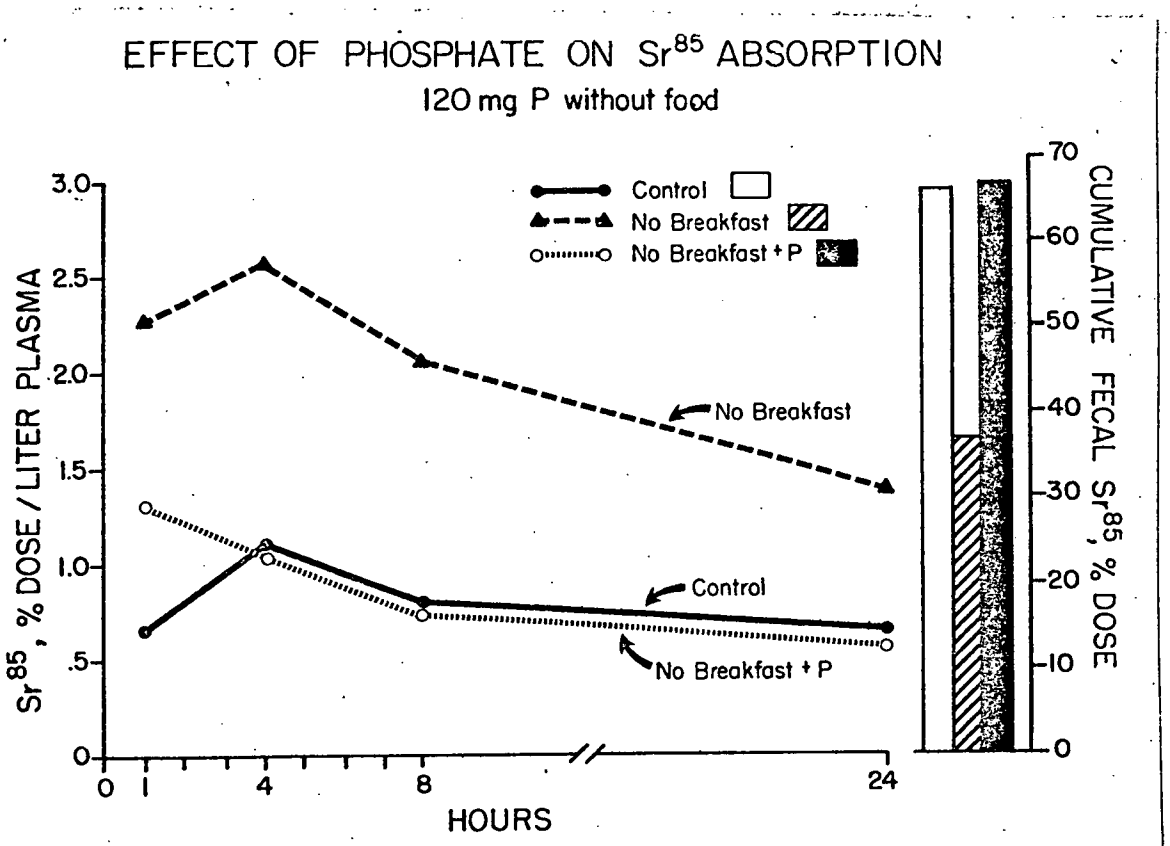


FIGURE 3



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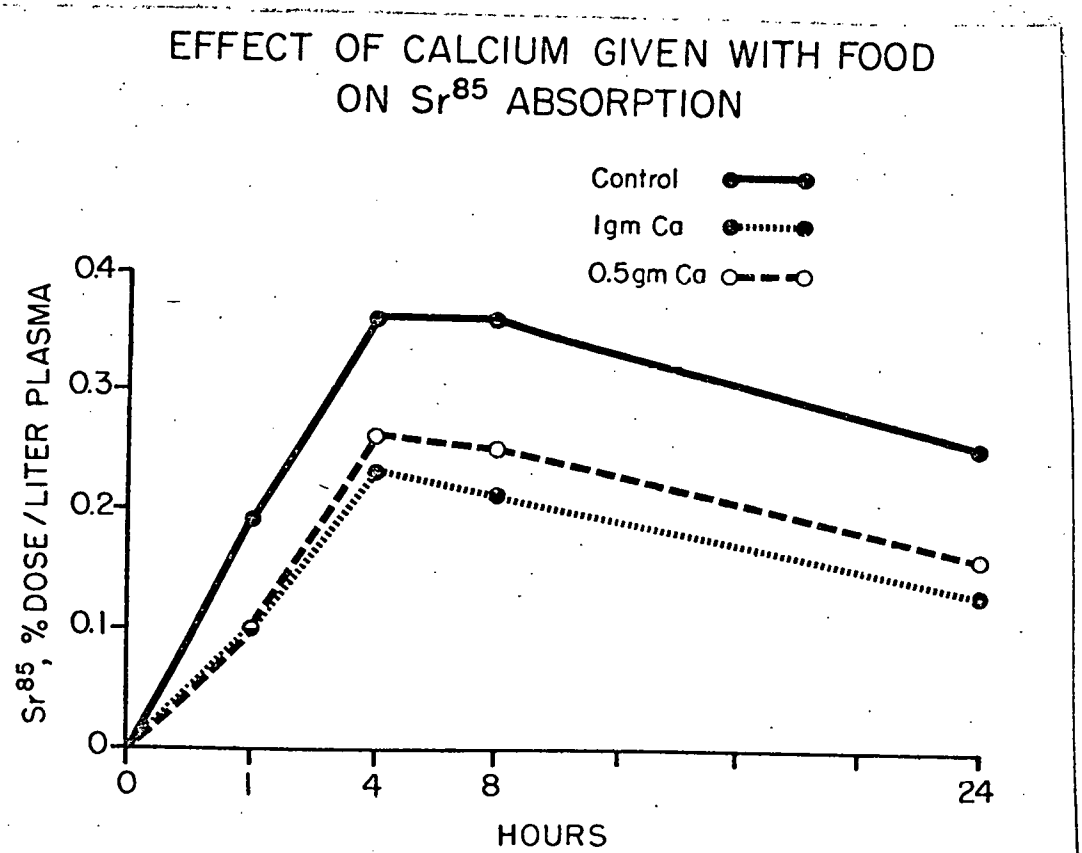

FIGURE 5

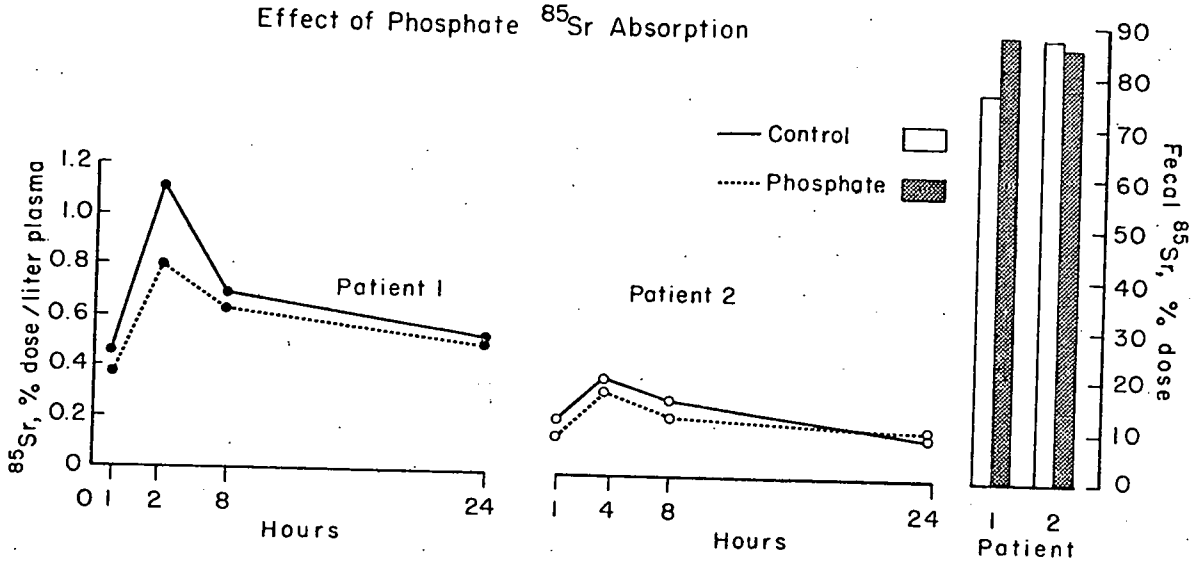

FIGURE 6

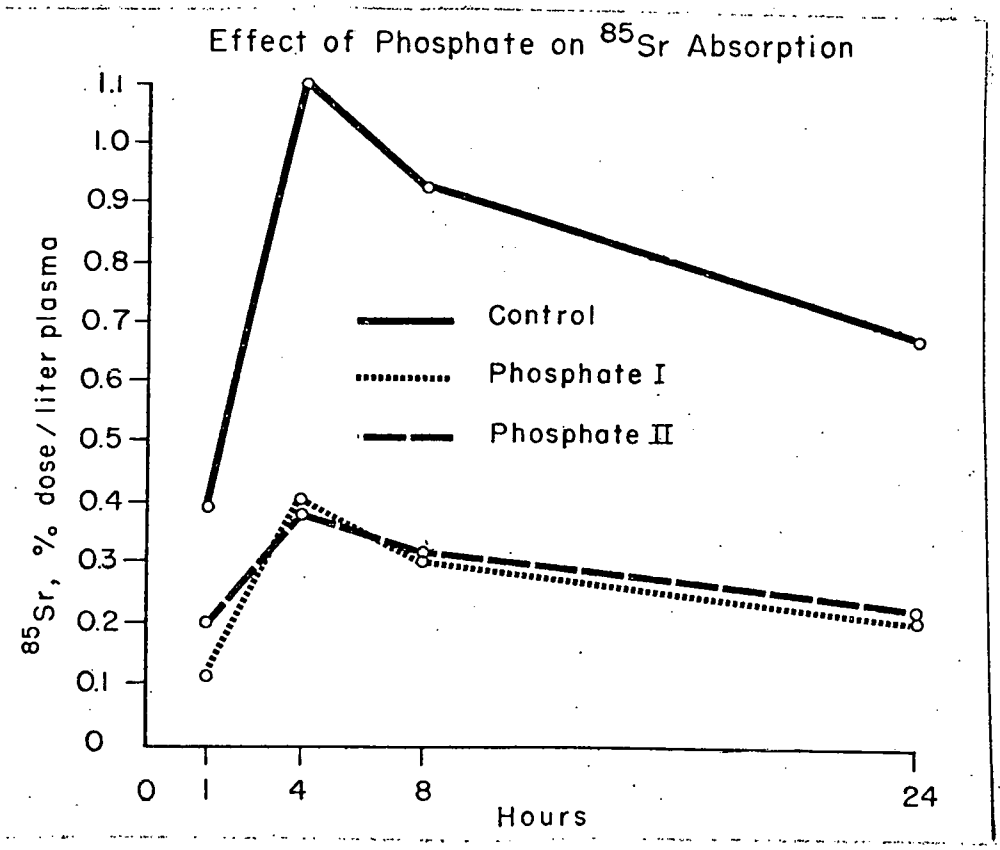

FIGURE 7

EFFECT OF A SINGLE DOSE OF CALCIUM AND OF CALCIUM AND PHOSPHOROUS ON Sr^{85} ABSORPTION

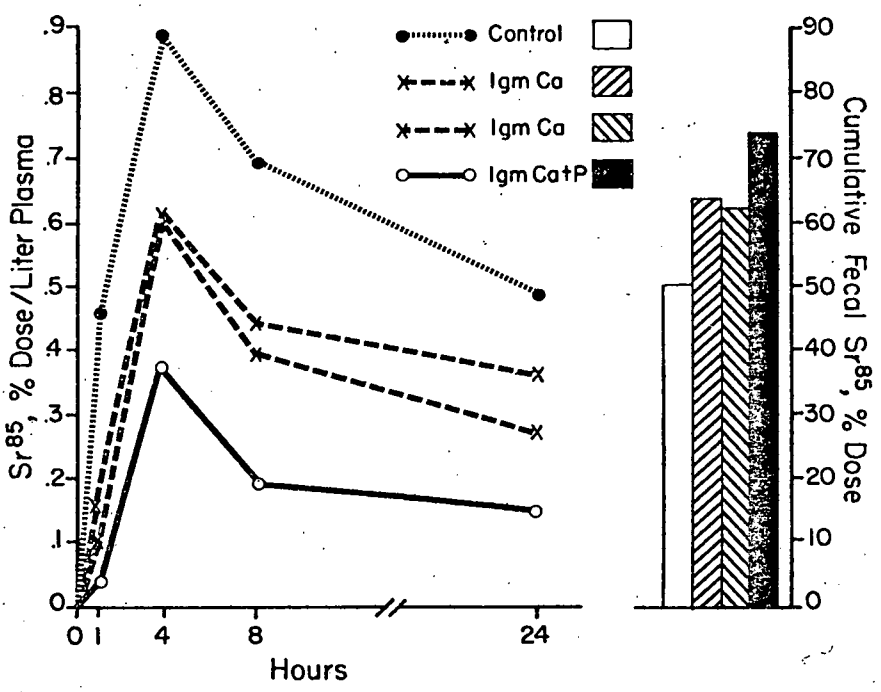

FIGURE 8

Sr^{85} PLASMA LEVELS IN HYPERMETABOLISM AND IN MYXEDEMA

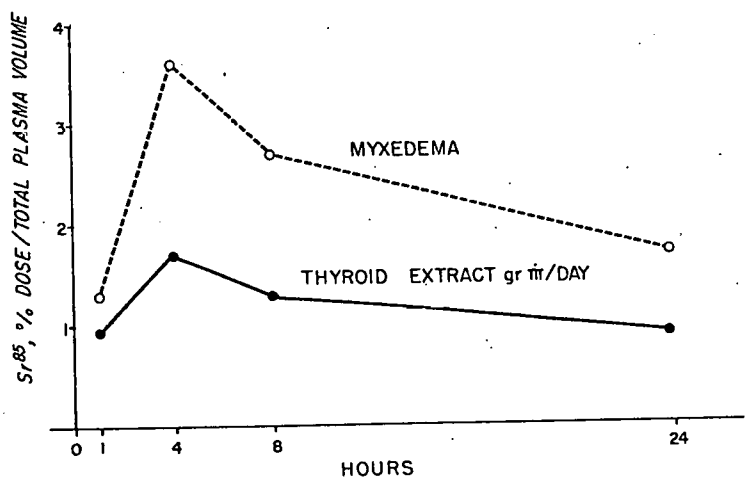

FIGURE 9

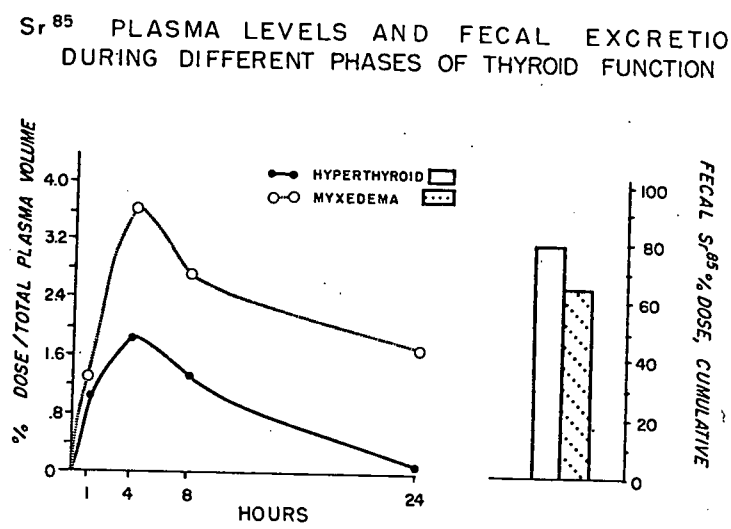

FIGURE 10

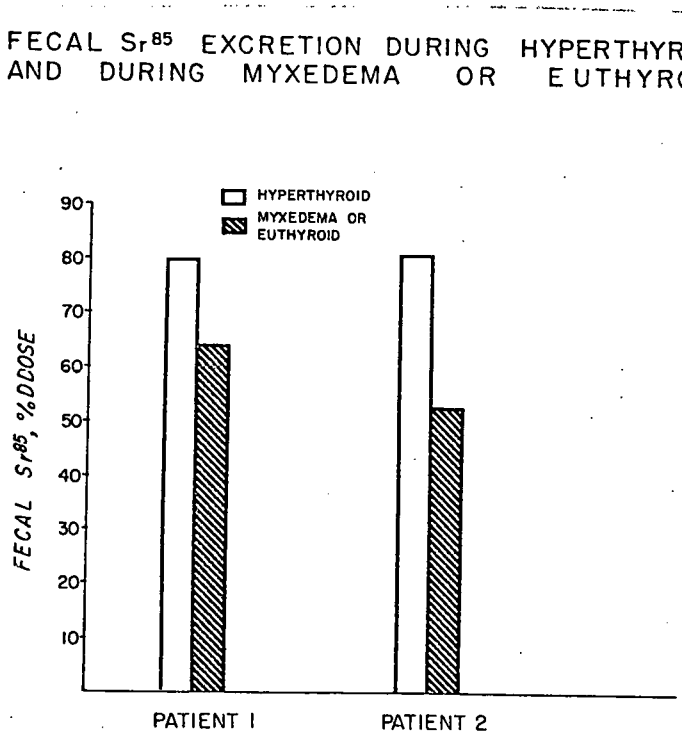

FIGURE 11

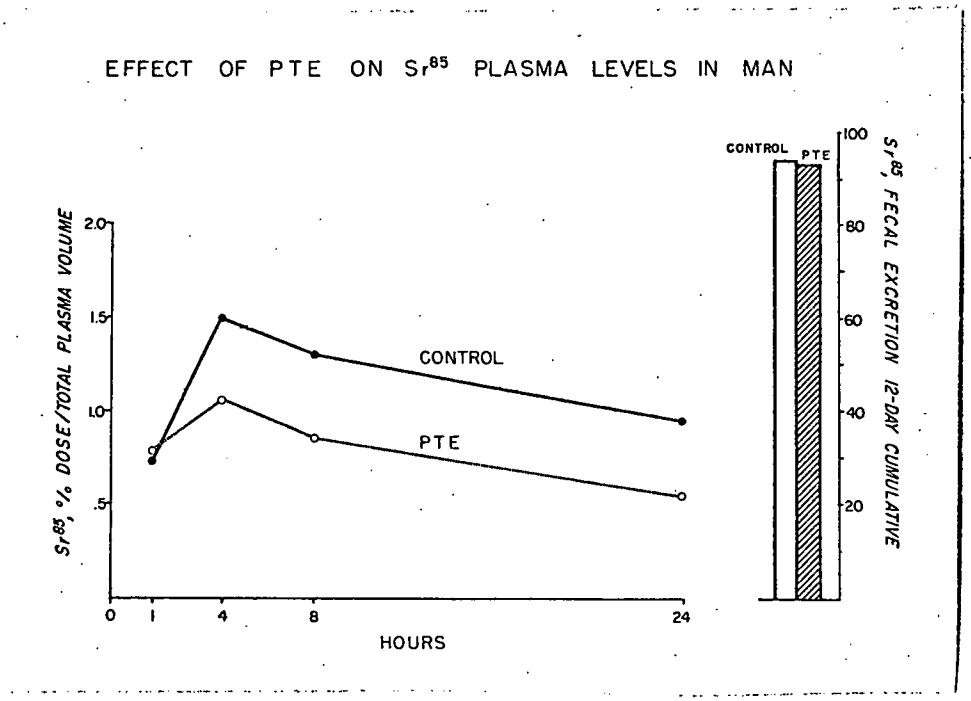

FIGURE 12

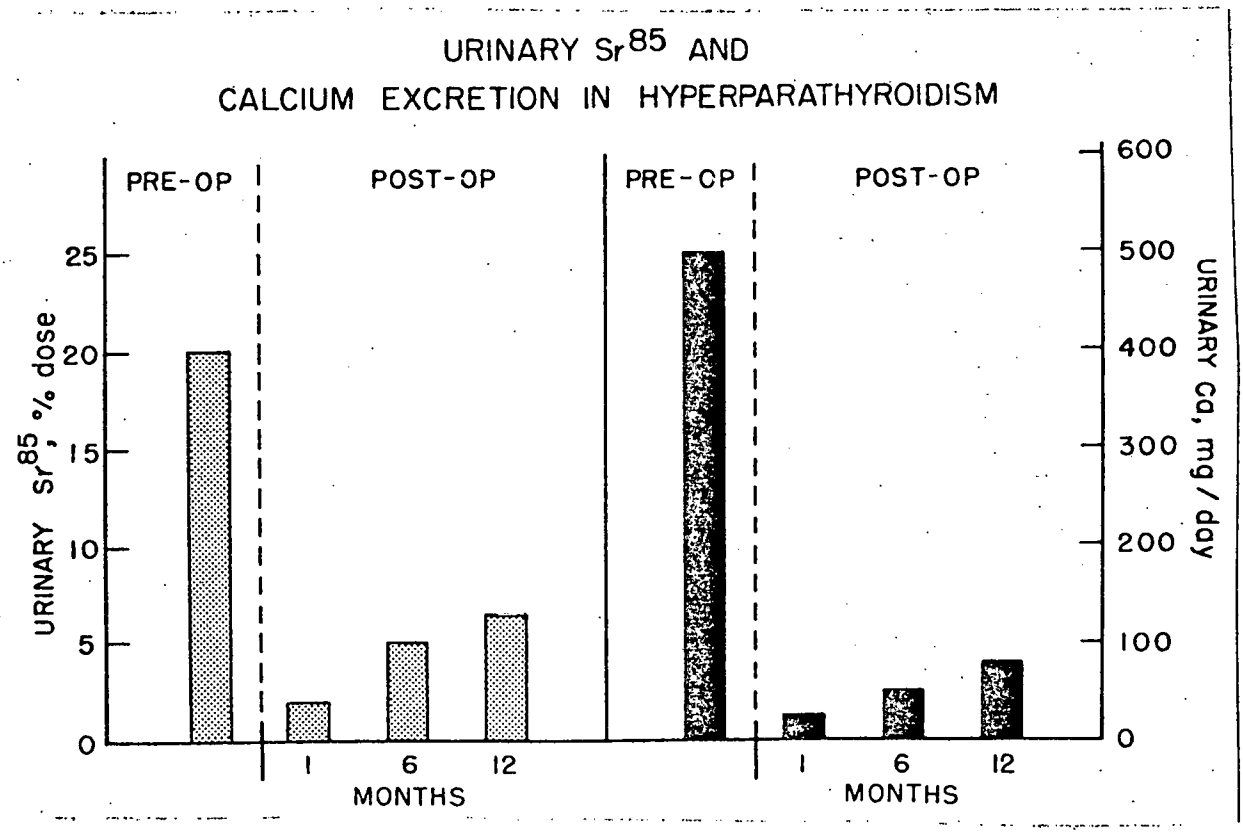

FIGURE 13

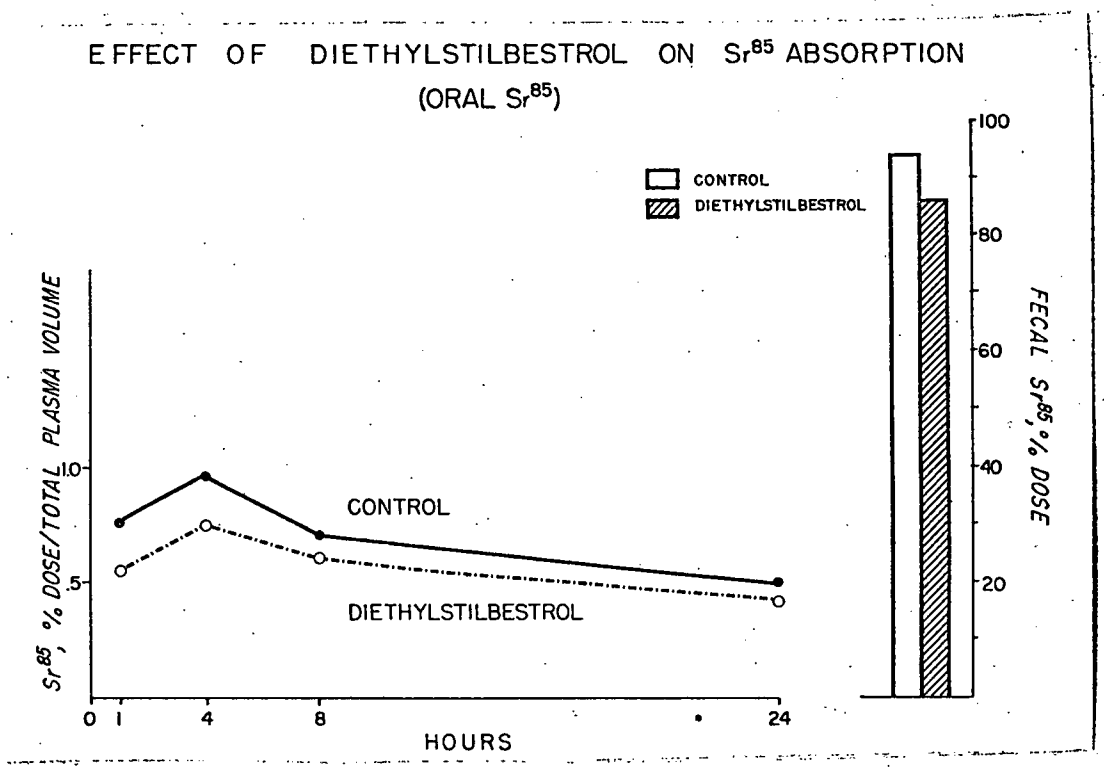
EFFECT OF DIETHYLSTILBESTROL ON Sr^{85} ABSORPTION
(ORAL Sr^{85})
CONTROL
DIETHYLSTILBESTROL
Sr^{85}, % DOSE/TOTAL PLASMA VOLUME
1.0
.5
CONTROL
DIETHYLSTILBESTROL
0
1
4
8
24
HOURS
100
80
60
40
20
FECAL Sr^{85}, % DOSE

TABLE 1

TRACE ELEMENT STUDIES CARRIED OUT DURING DIFFERENT CALCIUM INTAKES

PATIENT	CALCIUM INTAKE, mg/day			AGE	DIAGNOSIS	STUDY DAYS
	200 mg	800 mg	1300 mg			
1	+	+ +	+	67	Psychoneurosis	120
2	+ +	+ + +	+	47	Normal, psychoneurosis	180
3	+	+	+	60	Osteoporosis	90
4	+	+	-	52	Osteoporosis	60
5	-	+	-	38	Normal, psychoneurosis	30
6	-	+	-	54	Osteoporosis	30
7	-	+	+	56	Psychoneurosis	60
8	-	+	-	27	History of alcoholism	30
TOTAL	5	11	4			600

TABLE 2

COMPARATIVE TRACE ELEMENT ANALYSES OF DIET, URINE, AND STOOL DETERMINED IN DIFFERENT LABORATORIES

(1300 mg calcium intake)

TRACE ELEMENT ANALYSIS	PARTICIPATING LABORATORIES		
	Laboratory 1	Laboratory 2	Laboratory 3
Diet			
Cadmium, ng/g	4.6 ± 0.5	5.7	5.1 ± 0.1
Nickel, ng/g	90 ± 13	<100	72 ± 11
Lead, ng/g	83 ± 6	52 ± 8	120 ± 5
Zinc, µg/g	5.3 ± 0.3	4.1 ± 0.4	5.0 ± 0.3
Urine			
Cadmium, ng/g	1.4 ± 0.9	1.7 ± 1.0	1.3 ± 0.8
Nickel, ng/g	9 ± 4	<100	60 ± 18
Lead, ng/g	8.1 ± 4.6	< 10	7.6 ± 2.6
Zinc, µg/g	0.19 ± 0.06	0.20 ± 0.04	0.16 ± 0.03
Stool			
Cadmium, ng/g	14 ± 4	20 ± 6	35 ± 11
Nickel, ng/g	350 ± 80	<100	340 ± 84
Lead, ng/g	370 ± 130	92 ± 24	640 ± 220
Zinc, µg/g	40 ± 11	26 ± 7	40 ± 6

Number of samples analysed: Laboratory 1: 5 samples of diet, 19 samples of urine and stool
Laboratory 2: 3 samples of diet, 12 samples of urine and stool
Laboratory 3: 3 samples of diet, 12 samples of urine and stool

TABLE 3

COMPARATIVE TRACE ELEMENT ANALYSES OF DIET, URINE, AND STOOL DETERMINED IN DIFFERENT LABORATORIES

(800 mg calcium intake)

TRACE ELEMENT ANALYSIS	PARTICIPATING LABORATORIES		
	Laboratory 1	Laboratory 4	Laboratory 5
Diet			
Cadmium, ng/g	4.5 ± 0.8	5.3 ± 0.6	4.1 ± 0.5
Nickel, ng/g	110 ± 11	60 ± 5	71 ± 11
Lead, ng/g	110 ± 14	60 ± 5	6.7 ± 0.8
Zinc, µg/g	6.0 ± 0.5	6.1 ± 0.1	6.5 ± 0.8
Urine			
Cadmium, ng/g	1.0 ± 0.7	0.7 ± 0.5	0.6 ± 0.1
Nickel, ng/g	19 ± 9	16 ± 4	14 ± 4
Lead, ng/g	10 ± 4	10 ± 6	3.6 ± 0.5
Zinc, µg/g	0.24 ± 0.13	0.22 ± 0.14	0.17 ± 0.02
Stool			
Cadmium, ng/g	27 ± 11	39 ± 15	14 ± 1
Nickel, ng/g	460 ± 270	690 ± 530	468 ± 216
Lead, ng/g	360 ± 120	680 ± 280	188 ± 46
Zinc, µg/g	46 ± 9	49 ± 6	52 ± 5

Number of samples analyzed: Laboratory 1: 5 samples of diet and 20 samples of urine and stool
Laboratory 4: 3 samples of diet and 16 samples of urine and stool
Laboratory 5: 3 samples of diet and 4 samples of urine and stool

TABLE 4

PER CENT RECOVERY OF TRACE METALS IN HUMAN METABOLIC BALANCE SAMPLES

Element	1300 mg Ca per day				800 mg Ca per day			
	Participating Laboratory	Urine	Stool	Diet	Participating Laboratory	Urine	Stool	Diet
Cadmium	1	- 80	77	78	1	152	- 43	120
		50	77	-		161	- 12	105
						150	- 99	-
	2	40	26	-		302	-275	-
		111	24	-				
		123	39	-	4	92	195	-
						75	- 27	-
	3	59	20	-		-	123	-
		178	57	-				
		153	47	-	5	78	40	47
Copper	1	95	105	100				
		90	101	-				
Zinc	1	150	101	104	1	111	99	102
		5	236	-		101	114	107
						96	119	-
	2	72	86	-		106	107	-
		102	78	-				
		102	108	-	4	88	206	-
						96	48	-
	3	101	112	-		69	160	-
		99	75	-				
		92	111	-	5	100	95	140
Lead	1	- 71	70	101	1	143	103	75
		- 36	61	-		208	48	100
						136	36	-
	2	-	16	-		32	17	-
		-	46	-				
		-	15	-	4	31	174	-
						119	- 30	-
	3	78	129	-		67	68	-
		76	122	-				
		68	200	-	5	5	0	- 1
Manganese	1	75	108	95				
		0	138	-				
Nickel	1	105	99	97	1	63	78	101
		- 30	92	-		134	78	102
						174	74	-
	2	-	-	-		280	40	-
	3	50	186	-	4	101	239	-
		2	154	-		103	95	-
		27	185	-		92	113	-

TABLE 5

CADMIUM, COPPER, AND ZINC BALANCES DURING AN 800 mg INTAKE OF CALCIUM

PATIENT	PERIOD (6 days)	CADMIUM, µg/day				COPPER, µg/day				ZINC, mg/day			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
1	1	13.00	3.43	5.04	4.53	1003.2	110.09	969.00	- 75.89	12.79	0.50	11.71	+0.58
	2	9.55	2.74	3.63	3.18	954.66	104.79	751.68	+ 98.19	13.21	0.54	8.93	+3.74
	3	10.68	3.92	3.72	3.04	931.93	106.28	1931.58*	-1105.93*	12.89	0.56	12.59	-0.26
	4	10.23	3.03	4.18	3.02	977.39	143.98	1022.91	- 189.5	15.50	0.69	10.80	+4.01
	5	7.73	2.41	5.02	0.30	931.73	137.33	1367.52	- 573.12	13.68	0.65	11.66	+1.37
	Average	10.24	3.11	4.32	2.81	959.78	120.49	1027.78	- 188.49	13.61	0.59	11.14	+1.88
	SD	1.91	0.59	0.68	1.54	30.76	18.65	255.04	284.46	±1.11	±0.08	±1.39	±1.91
2	1	13.00	4.35	8.67	-0.02	1003.2	132.07	1250.96	- 379.96	12.79	0.70	14.39	-2.30
	2	9.55	5.72	5.93	-2.10	954.66	116.92	1089.81	- 252.07	13.21	0.69	11.44	+1.08
	3	10.68	1.50	7.79	1.39	931.93	108.33	1200.85	- 377.25	12.89	0.67	13.86	-1.64
	4	10.23	4.10	6.52	-0.39	977.39	124.20	1652.69	- 799.50	15.50	1.01	13.09	+1.40
	5	7.73	1.71	6.71	-0.69	931.73	115.52	2852.59*	-2036.38*	13.68	0.72	14.41	-1.45
	Average	10.24	3.48	7.12	-0.36	959.78	119.41	1298.58	- 458.21	13.61	0.76	13.44	-0.59
	SD	1.91	1.82	1.09	1.26	30.76	9.05	245.49	239.11	±1.11	±0.14	±1.24	±1.70
7	1	13.00	6.50	7.70	-1.20	1003.2	104.50	841.33	+ 57.37	12.79	0.64	11.41	+0.74
	2	9.55	6.08	8.54	-5.17	954.66	179.34	998.47	- 223.15	13.21	0.66	12.81	-0.26
	3	10.68	1.15	7.68	1.85	931.93	111.36	974.13	- 153.56	12.89	0.54	12.88	-0.53
	4	10.23	4.60	5.28	0.35	977.39	158.47	1387.82*	- 568.90*	15.50	0.52	10.78	+4.20
	5	7.73	7.48	5.97	-5.72	931.73	139.31	922.77	- 130.35	13.68	0.57	11.37	+1.74
	Average	10.24	5.18	7.03	-1.98	959.78	138.60	934.18	- 113.00	13.61	0.59	11.85	+1.17
	SD	1.91	2.48	1.35	3.35	30.76	31.46	69.48	119.87	±1.11	±0.06	±0.94	±1.92
8	1	13.00	0.94	7.07	4.99	1003.2	70.70	3348.23*	-2415.73*	12.79	0.97	11.08	+0.74
	2	9.55	0.18	9.33	0.04	954.66	91.54	1190.21	- 327.09	13.27	1.08	8.49	+3.70
	3	10.68	0.46	9.40	0.82	931.93	86.56	1206.63	- 361.26	12.89	0.99	8.15	+3.75
	4	10.23	2.60	7.26	0.37	977.39	95.07	1740.21	- 857.89	15.50	1.22	10.18	+4.10
	5	7.73	8.48	7.68	-8.43	931.73	113.91	1494.35	- 676.53	13.68	1.21	10.08	+2.39
	Average	10.24	2.53	8.15	-0.44	959.78	91.56	1407.85	- 539.63	13.63	1.09	9.60	+2.94
	SD	1.91	3.45	1.13	4.89	30.76	15.59	261.92	255.60	±1.11	±0.12	±1.23	±1.39
Overall (N=20)	Average	10.24	3.57	6.66	0.01	959.78	117.51	1167.10	- 324.83	13.62	0.76	11.51	+1.35
	SD	1.91	2.37	1.77	3.38	30.76	25.44	222.79	211.46	±1.11	±0.23	±1.80	±2.07

* Values omitted from the individual averages and from the overall average because of obvious deviation from the other analyzed values.

TABLE 6

LEAD, MANGANESE, AND NICKEL BALANCES DURING A CALCIUM INTAKE OF 800 mg PER DAY

PATIENT	PERIOD (6 days)	LEAD, µg/day				MANGANESE, µg/day				NICKEL, µg/day			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
1	1	209.76	26.11	81.46	102.19	2143.20	6.92	1256.38	879.90	273.60	62.91	59.38	151.31
	2	211.39	28.66	70.81	111.92	2227.54	8.63	1071.00	1147.91	250.03	61.64	47.80	140.59
	3	275.03	26.42	121.11	127.50	2068.43	0.91	1386.27	681.25	295.49	81.99	155.27	58.23
	4	261.40	25.43	77.85	158.12	2045.70	0.92	1381.28	663.50	250.03	44.42	71.20	134.41
	5	259.07	30.52	106.34	122.21	2045.70	1.83	1740.48	303.39	227.27	33.57	105.67	88.03
	Average	243.33	27.43	91.51	124.39	2106.11	3.84	1367.08	735.19	259.28	56.91	87.86	114.51
	SD	30.52	2.11	21.28	21.22	78.80	3.66	244.91	310.55	26.04	18.63	43.46	39.68
2	1	209.76	28.54	106.71	74.51	2143.20	10.22	1998.33	134.65	273.60	53.25	79.93	140.42
	2	211.39	24.25	93.08	94.06	2227.54	5.20	1753.01	469.33	250.03	49.80	80.28	119.95
	3	275.03	32.08	109.69	133.26	2068.43	1.25	1951.39	115.79	295.49	58.33	151.84	85.32
	4	261.40	30.22	97.51	133.67	2045.70	4.14	1796.09	245.47	250.03	66.24	153.44	30.35
	5	259.07	32.52	77.00	149.53	2045.70	4.71	1953.57	87.42	227.27	53.48	103.56	70.23
	Average	243.33	29.52	96.80	117.01	2106.11	5.10	1890.48	210.53	259.28	56.22	113.81	89.25
	SD	30.52	3.35	12.95	31.36	78.80	3.25	108.55	156.59	26.04	6.37	36.72	43.03
7	1	209.76	28.64	59.24	121.88	2143.20	20.90	1516.69	605.61	273.60	59.99	63.16	150.45
	2	211.39	31.88	68.78	110.73	2227.54	3.19	1539.21	685.14	250.03	59.58	73.05	117.20
	3	275.03	33.01	82.66	159.36	2068.43	3.58	1475.25	589.60	295.49	55.68	77.51	162.30
	4	261.40	32.88	78.23	150.29	2045.70	4.36	1417.99	623.35	250.03	59.43	121.11	69.49
	5	259.07	32.24	58.38	168.45	2045.70	7.56	1451.95	586.19	227.27	111.45	73.91	41.91
	Average	243.33	31.73	69.46	142.14	2106.11	7.92	1480.22	617.97	259.28	69.27	81.75	108.27
	SD	30.52	1.79	10.94	24.76	78.80	7.46	48.75	40.34	26.04	23.65	22.64	51.68
8	1	209.76	43.60	99.32	66.84	2143.20	1.89	2026.51	114.80	273.60	40.06	232.45	1.09
	2	211.39	36.61	70.32	104.46	2227.54	1.83	2087.16	138.55	250.03	28.77	108.56	112.70
	3	275.03	43.55	99.18	132.30	2068.43	3.25	2549.47	-484.29	295.49	108.20	112.80	74.49
	4	261.40	38.49	100.28	122.63	2045.70	3.71	2385.48	-343.49	250.03	83.47	189.31	-22.75
	5	259.07	44.60	109.10	105.37	2045.70	5.09	2260.68	-220.07	227.27	82.40	167.59	-22.72
	Average	243.33	41.37	95.64	106.32	2106.11	3.15	2261.86	-158.90	259.28	68.58	162.14	28.56
	SD	30.52	3.57	14.75	25.02	78.80	1.36	214.43	277.07	26.04	33.09	52.48	61.66
Overall	Average	243.33	32.51	88.35	122.47	2106.11	5.00	1749.01	351.20	259.28	62.74	111.39	85.15
	SD	30.52	6.05	18.19	27.24	78.80	4.54	397.33	416.15	26.04	21.68	49.25	57.44

TABLE 7

CADMIUM, COPPER, AND ZINC BALANCES DURING A 1300 mg CALCIUM INTAKE PER DAY

PATIENT	PERIOD (6 days)	CADMIUM, µg/day				COPPER, µg/day				ZINC, mg/day			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
1	1	13.78	5.87	3.04	4.87	661.44	92.70	638.56	- 69.82	14.06	0.68	11.67	+1.71
	2	11.58	13.91	2.72	-5.05	675.47	101.44	506.63	67.40	14.07	0.81	9.03	+4.23
	3	11.87	4.78	4.41	2.68	745.07	188.38	555.84	0.85	15.67	0.93	20.74	-6.00
	4	14.09	6.48	3.20	4.41	718.12	98.64	465.08	154.40	14.09	0.65	10.70	+2.74
	5	11.02	3.23	2.41	5.38	716.56	80.65	615.21	20.70	15.65	0.56	11.19	+3.90
	Average	12.47	6.85	3.16	2.46	703.33	112.36	556.26	34.71	14.71	0.73	12.67	+1.31
	SD	1.38	4.13	0.76	4.32	34.16	43.24	72.50	83.16	±0.87	±0.14	±4.62	±4.21
2	1	13.78	4.97	3.95	4.86	661.44	144.90	726.95	-210.41	14.06	0.66	12.98	+0.42
	2	11.58	6.25	5.64	-0.31	675.47	136.62	618.83	- 79.98	14.07	0.78	10.28	+3.01
	3	11.87	3.48	6.96	1.43	745.07	116.15	566.70	62.22	15.67	0.62	12.17	+2.88
	4	14.09	2.45	5.65	5.99	718.12	114.29	696.69	- 92.86	14.09	0.61	12.71	+0.77
	5	11.02	2.82	4.55	3.65	716.56	112.84	660.44	- 56.72	15.65	0.69	10.76	+4.20
	Average	12.47	3.99	5.35	3.13	703.33	124.96	653.92	- 75.55	14.71	0.67	11.78	+2.26
	SD	1.38	1.59	1.16	2.56	34.16	14.76	63.33	97.26	±0.87	±0.07	±1.20	±1.61
3	1	13.78	2.00	2.52	9.26	661.44	57.22	677.62	- 73.40	14.06	0.31	13.66	+0.09
	2	11.58	2.11	3.21	6.26	675.47	63.26	588.01	24.20	14.07	0.48	11.98	+1.61
	3	11.87	1.94	5.73	4.20	745.07	55.33	689.17	0.57	15.67	0.39	13.92	+1.36
	4	14.09	2.10	5.18	6.81	718.12	60.03	794.31	-136.22	14.09	0.39	16.85	-3.15
	Average	12.83	2.04	4.16	6.63	700.03	58.96	687.28	- 46.21	14.47	0.39	14.10	-0.02
	SD	1.29	0.08	1.54	2.08	38.51	3.46	84.47	73.00	±0.80	±0.07	±2.02	±2.19
7	1	13.78	6.20	5.81	1.77	661.44	193.83	709.76	-242.15	14.06	0.74	12.06	+1.26
	2	11.58	4.34	3.97	3.27	675.47	94.68	597.64	- 16.85	14.07	0.59	10.66	+2.82
	3	11.87	4.52	5.07	2.28	745.07	131.83	558.83	54.41	15.67	0.57	10.54	+4.56
	4	14.09	8.32	5.28	0.49	718.12	105.89	736.15	-123.92	14.09	1.10	13.36	-0.37
	5	11.02	6.03	3.25	1.74	716.56	79.10	822.51	-185.05	15.65	0.60	11.92	+3.13
	Average	12.47	5.88	4.68	1.91	703.33	121.07	684.98	-102.72	14.71	0.72	11.71	+2.28
	SD	1.38	1.60	1.04	1.01	34.16	44.99	106.87	121.17	±0.87	±0.22	±1.16	±1.89
Overall	Average	12.54	4.83	4.34	3.37	702.64	106.73	643.42	- 47.51	14.65	0.63	12.57	+1.45
	SD	1.25	2.88	1.33	3.12	32.04	33.15	83.33	103.60	±0.79	±0.19	±2.63	±2.64

TABLE 8

LEAD, MANGANESE, AND NICKEL BALANCES DURING A CALCIUM INTAKE OF 1300 mg PER DAY

PATIENT	PERIOD (6 days)	LEAD, µg/day				MANGANESE, µg/day				NICKEL, µg/day			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
1	1	209.46	23.79	87.19	98.48	1626.04	3.09	1427.55	195.40	300.40	27.81	77.36	195.23
	2	231.59	54.78	68.90	107.91	1626.63	8.70	1178.27	439.66	232.97	23.19	83.09	126.69
	3	218.00	33.46	88.13	96.41	1655.70	2.81	1425.60	227.29	206.96	64.67	108.86	33.43
	4	256.87	12.96	74.74	169.17	1657.20	2.82	1166.74	487.64	259.63	25.37	78.77	155.49
	5	228.75	14.25	108.94	105.56	1626.04	2.69	1247.45	375.90	259.06	26.88	81.70	150.48
	Average	228.93	27.85	85.58	115.51	1638.32	4.02	1289.12	345.18	251.80	33.58	85.96	132.26
	SD	17.93	17.17	15.42	30.38	16.56	2.62	129.22	128.94	34.79	17.47	13.00	60.49
2	1	209.46	45.13	115.97	48.36	1626.04	4.14	1474.67	147.23	300.40	28.98	86.20	185.22
	2	231.59	42.55	113.39	75.65	1626.63	9.76	1488.33	128.54	232.97	31.23	130.62	71.12
	3	218.00	25.94	109.92	82.14	1655.70	3.87	1608.81	43.02	206.96	30.97	143.77	32.22
	4	256.87	22.86	119.18	114.83	1657.20	4.08	1551.11	102.01	259.63	36.74	147.22	75.67
	5	228.75	24.18	90.06	114.51	1626.04	4.03	1340.89	281.12	259.06	28.21	107.57	123.28
	Average	228.93	32.13	109.70	87.10	1638.32	5.18	1492.76	140.38	251.80	31.23	123.08	97.50
	SD	17.93	10.78	11.50	28.18	16.56	2.56	100.35	87.96	34.79	3.34	25.83	58.72
3	1	209.46	10.01	143.02	56.43	1626.04	2.86	1221.32	401.86	300.40	14.30	78.74	207.36
	2	231.59	11.81	97.23	122.55	1626.63	2.81	1160.59	463.23	232.97	12.65	141.52	78.80
	3	218.00	9.68	111.33	96.99	1655.70	2.77	1461.18	191.75	206.96	16.60	139.16	51.20
	4	256.87	10.51	136.00	110.36	1657.20	3.00	1516.41	137.79	259.63	12.01	134.79	112.83
	Average	228.98	10.50	121.90	96.58	1641.39	2.86	1339.88	298.66	249.99	13.89	123.55	112.55
	SD	20.71	0.94	21.33	28.73	17.40	0.10	175.19	158.16	39.90	2.05	30.00	68.05
7	1	209.46	67.84	128.30	13.32	1626.04	11.63	1387.25	227.16	300.40	42.64	109.44	148.32
	2	231.59	29.19	131.57	70.83	1626.63	3.95	1190.82	431.86	232.97	43.40	93.21	96.36
	3	218.00	20.72	126.30	70.98	1655.70	3.77	1281.22	370.71	206.96	41.43	94.05	71.48
	4	256.87	54.46	165.04	37.37	1657.20	7.56	1406.99	242.65	259.63	37.82	112.20	109.61
	5	228.75	26.37	131.32	71.06	1626.04	3.77	1390.32	231.95	259.06	26.37	97.44	135.25
	Average	228.93	39.72	136.51	52.71	1638.32	6.14	1331.32	300.87	251.80	38.33	101.27	112.20
	SD	17.93	20.36	16.10	26.39	16.56	3.47	92.99	94.35	34.79	7.02	8.92	30.63
Overall	Average	228.94	28.45	112.98	87.52	1638.97	4.64	1364.50	269.83	251.42	30.07	107.67	113.69
	SD	16.91	17.16	24.47	35.30	15.34	2.61	124.83	135.07	32.75	12.76	24.86	52.24

TABLE 9

COMPARATIVE CADMIUM, COPPER, AND ZINC BALANCES DURING DIFFERENT CALCIUM INTAKES

PATIENT		800 mg CALCIUM PER DAY				1300 mg CALCIUM PER DAY			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
		CADMIUM BALANCES							
1	Average	10.24	3.11	4.32	2.81	12.47	6.85	3.16	2.46
	SD	1.91	0.59	0.68	1.54	1.38	4.13	0.76	4.32
2	Average	10.24	3.48	7.12	- 0.36	12.47	3.99	5.35	3.13
	SD	1.91	1.82	1.09	1.26	1.38	1.59	1.16	2.56
7	Average	10.24	5.18	7.03	- 1.98	12.47	5.88	4.68	1.91
	SD	1.91	2.48	1.35	3.35	1.38	1.60	1.04	1.01
		COPPER BALANCES							
1	Average	959.78	120.49	1,208.54	- 369.25	703.33	112.36	556.26	34.71
	SD	30.76	18.65	460.60	479.88	34.16	43.24	72.50	83.16
2	Average	959.78	119.41	1,609.38	- 769.01	703.33	124.96	653.92	- 75.55
	SD	30.76	9.05	726.77	738.13	34.16	14.76	63.33	97.26
7	Average	959.78	138.60	1,024.90	- 203.72	703.33	121.07	684.98	- 102.72
	SD	30.76	31.46	211.61	229.02	34.16	44.99	106.87	121.17
		ZINC BALANCES							
1	Average	13,613.43	588.73	11,135.98	1888.72	14,708.9	726.39	12,663.9	1318.6
	SD	1,111.27	77.99	1,389.34	1908.81	872.0	143.45	4,620.2	4205.5
2	Average	13,613,43	760.83	13,437.00	- 584.40	14,708.9	671.98	11,779.4	2257.48
	SD	1,111.27	143.36	1,239.28	1696.16	872.0	67.83	1,198.6	1613.13
7	Average	13,613.43	583.46	11,848.32	1181.65	14,708.9	718.53	11,707.1	2283.29
	SD	1,111.27	62.43	942.63	1916.03	872.0	221.58	1,156.7	1891.99

TABLE 10

COMPARATIVE LEAD, MANGANESE, AND NICKEL BALANCES DURING DIFFERENT CALCIUM INTAKES

PATIENT		800 mg CALCIUM PER DAY				1300 mg CALCIUM PER DAY			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
		LEAD BALANCES							
1	Average	243.33	27.43	91.51	124.39	228.93	27.85	85.58	115.51
	SD	30.52	2.11	21.28	21.22	17.93	17.17	15.42	30.38
2	Average	243.33	29.52	96.80	117.01	228.93	32.13	109.70	87.10
	SD	30.52	3.35	12.95	31.36	17.93	10.78	11.50	28.18
7	Average	243.33	69.46	69.46	142.14	228.93	39.72	136.51	52.71
	SD	30.52	10.94	10.94	24.76	17.93	20.36	16.10	26.39
		MANGANESE BALANCES							
1	Average	2106.11	3.84	1367.08	735.19	1638.32	4.02	1289.12	345.18
	SD	78.80	3.66	244.91	310.55	16.56	2.62	129.22	128.94
2	Average	2106.11	5.10	1890.48	210.53	1638.32	5.18	1492.76	140.38
	SD	78.80	3.25	108.55	156.59	16.56	2.56	100.35	87.96
7	Average	2106.11	7.92	1480.22	617.97	1638.32	6.14	1331.32	300.87
	SD	78.80	7.46	48.75	40.34	16.56	3.47	92.99	94.35
		NICKEL BALANCES							
1	Average	259.28	56.91	87.86	114.51	251.80	33.58	85.96	132.26
	SD	26.04	18.63	43.46	39.68	34.79	17.47	13.00	60.49
2	Average	259.28	56.22	113.81	89.25	251.80	31.23	123.08	97.50
	SD	26.04	6.37	36.72	43.03	34.79	3.34	25.83	58.72
7	Average	259.28	69.27	81.75	108.27	251.8	38.33	101.27	112.20
	SD	26.04	23.65	22.64	51.68	34.79	7.02	8.92	30.63

TABLE 11

CADMIUM, COPPER, AND ZINC BALANCES DETERMINED DURING A LOW CALCIUM INTAKE

PATIENT	STUDY DAYS	CADMIUM, µg/day*				COPPER, µg/day*				ZINC, mg/day*			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
2	6	9.9	3.9	8.6	- 2.6	826	87	700	+ 39	15.9	0.6	12.2	+ 3.1
	6	7.9	3.9	8.7	- 4.7	920	93	805	+ 22	15.8	0.6	12.3	+ 2.9
	6	11.9	3.3	7.9	+ 0.7	952	79	788	+ 85	15.2	0.6	12.1	+ 2.5
	6	9.9	2.1	7.2	+ 0.6	894	81	787	+ 26	15.8	0.6	11.6	+ 3.6
	6	11.9	3.8	10.7	- 2.6	891	111	832	- 52	16.1	0.6	13.7	+ 1.8
Average	30	10.3	3.4	8.6	- 1.7	897	90	782	+ 25	15.8	0.6	12.4	+ 2.8
3	6	9.9	2.5	5.6	+ 1.8	826	86	797	- 57	13.6	0.5	11.3	+ 1.8
	6	7.9	3.6	5.9	- 1.6	920	82	645	+193	13.5	0.4	13.8	- 0.7
	6	11.9	1.9	5.3	+ 4.7	952	74	656	+222	14.6	0.5	10.0	+ 4.1
	6	9.9	2.5	4.7	+ 2.7	894	88	707	+ 99	13.6	0.5	12.8	+ 0.3
	6	11.9	3.1	8.7	+ 0.1	891	95	783	+ 13	13.4	0.5	11.1	+ 1.0
Average	30	10.3	2.7	6.1	+ 1.5	897	85	718	+ 94	13.7	0.5	11.9	+ 1.3

* Values are averages for each 6-day study period

TABLE 12

LEAD, MANGANESE, AND NICKEL BALANCES DETERMINED DURING A LOW CALCIUM INTAKE

PATIENT	STUDY DAYS	LEAD, µg/day*				MANGANESE, µg/day*				NICKEL, µg/day*			
		Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance	Diet	Urine	Stool	Balance
2	6	182	48	56	+ 78	2199	9	2180	+ 10	257	139	157	- 39
	6	224	31	59	+134	2236	13	2301	- 78	277	138	240	-101
	6	206	37	45	+124	2366	8	2306	+ 52	257	150	148	- 41
	6	220	34	32	+154	2161	9	2048	+104	278	206	118	- 46
	6	218	30	50	+138	2197	13	2465	-281	277	188	188	- 99
Average	30	210	36	49	+125	2232	11	2260	- 39	269	164	170	- 65
3	6	182	32	46	+104	2199	14	1075	+1110	257	143	122	- 8
	6	224	32	56	+136	2236	18	1470	+748	277	129	161	- 13
	6	206	32	29	+145	2366	6	928	+1432	257	103	92	+ 62
	6	220	39	40	+141	2161	14	1061	+1086	278	126	99	+ 53
	6	218	44	38	+136	2197	14	1663	+520	277	163	112	+ 2
Average	30	210	36	42	+132	2232	13	1240	+979	269	133	117	+ 19

* Values are averages for each 6-day study period

TABLE 13

CALCIUM AND PHOSPHORUS BALANCES DURING LOW, NORMAL, AND INTERMEDIATE CALCIUM INTAKES

PATIENT	STUDY DAYS	CALCIUM, mg/day*				PHOSPHORUS, mg/day*			
		Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
				Low Calcium Intake					
2	30	233	68	216	- 51	923	635	224	+ 64
3	30	225	11	241	- 27	716	470	230	+ 16
Average	30	229	40	229	- 40	820	553	227	+ 40
				Normal Calcium Intake					
1	36	796	298	511	- 13	1104	846	257	+ 1
2	30	799	126	679	- 6	1155	932	336	-113
7	30	774	304	571	-101	1111	846	394	-129
8	54	794	233	655	- 94	1148	751	402	- 5
Average	38	791	240	604	- 53	1130	844	348	- 62
S.E.M.		± 5	±41	±38	± 25	±12	±36	±33	± 34
				Intermediate Calcium Intake					
2	36	1330	95	1182	+ 53	1626	1038	516	+ 72
3	30	1256	22	1244	- 10	1450	698	583	+169
7	36	1300	250	885	+165	1559	1098	326	+135
8	30	1271	229	994	+ 48	1533	925	447	+161
Average	33	1289	149	1076	+ 64	1542	940	468	+134
S.E.M.		±16	±54	±82	± 36	±36	±88	±54	± 21

* Values are averages for the number of days indicated. The normal and intermediate calcium intakes were due to the addition of milk to the diet.