Studies on the Inhibition of Intestinal Absorption of Radioactive Strontium

III. The Effect of Administration of Sodium Alginate in Food and in Drinking Water

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ABSTRACT

A method is reported which permits selective suppression of absorption of radioactive strontium from ingested food material, permitting calcium to be available to the body. Studies were carried out by measuring bone uptake of Sr^{89} and Ca^{45} when various amounts of sodium alginate were fed with the diet. Long-term studies were made in which two different levels of radioactivity were used, to determine the pattern of Sr^{89} deposition with continuous intake of binding agent. It was found that administration of sodium alginate as a jelly overcomes the problem of constipation and effectively reduces Sr^{89} uptake, up to 83%. This fact represents a significant finding with respect to the use of the compound in human subjects. Addition of sodium alginate to drinking water is effective with low levels of Sr^{89} intake.

This naturally occurring water-soluble macromolecular substance possesses several advantages in use for the suppression of absorption of radioactive strontium when compared with synthetic ion exchange resins: there is no disturbance of electrolyte balance; efficiency is not reduced by treatment over a prolonged period of time; and finally, the product is palatable.

SOMMAIRE

Une methode est rapportée permettant la suppression sélective de l'absorption du strontium radioactif à partir des aliments ingérés, laissant le calcium disponible dans l'organisme.

Des études ont été faites en mesurant la déposition du Sr^{89} et du Ca^{45} dans les os, quand differentes quantités d'alguinate de sodium sont ajoutées à la diète.

Après des études de longues durées, utilisant deux differents niveaux de radioactivité pour déterminer le mode de déposition du Sr^{89} avec ingestion continuelle d'agent absorbant, on a constaté que: l'administration d'alguinate de sodium sous forme de gelée, résoud le problème de la constipation et réduit avec efficacité, l'absorption du Sr^{89}, jusqu'à 83%. L'addition d'alguinate de sodium à l'eau potable est efficace avec de petites quantités de Sr^{89} ingérés.

Cette substance macromoleculaire naturelle, soluble dans l'eau, possède plusieurs avantages quand on la compare à des résines synthetiques d'échange ionique, utilisés pour la suppression de l'absorption du strontium radioactif; il n'y a pas de perturbation de la balance électrolytique; son efficacité n'est pas reduite par un traitement de longue dureé et, de plus, la substance est palliable.

THE ingestion of radiostrontium from fall-out presents a potential health hazard from accidents in industrial plants or in the event of nuclear weapons testing. Earlier studies have shown that the administration of sodium alginate, a water-soluble, non-absorbable acidic polysaccharide prepared from certain species of marine algae, effectively reduces the absorption of radioactive strontium when injected with the radioisotope into ligated segments of rats' intestine.[1] The preparation is also effective when introduced directly into the stomach by intubation.[2] Interference with calcium absorption was negligible. The present studies describe the effect of oral ingestion of various amounts of sodium alginate on Sr^{89} absorption. Long-term experiments were also carried out in which two different levels of radioactivity were used to determine the pattern of Sr^{89} deposition with continuous intake of the binding agent. Earlier problems with constipation as a result of feeding powdered sodium alginate have been overcome by dissolving the polysaccharide in water before administration. A parallel series of experiments using Ca^{45} was also performed in order to detect any development of calcium deficiency in young rats as a result of long-term feeding with sodium alginate.

MATERIALS AND METHODS

Sr^{89} and Ca^{45}, supplied by Atomic Energy of Canada Limited, were diluted with water to give the selected activity. Young male and female rats of the RVH strain, weighing 90-120 g., were used.

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Animals were fed on standard Purina laboratory chow and drinking water was given *ad libitum* except where otherwise stated.

Sodium Alginate

Two batches of commercial sodium alginate of equal efficiency were utilized throughout these experiments. Both batches were prepared from Pacific giant kelp. Samples from other sources were found to give varying results; the efficiency of alginate preparations from different species of brown algae is under investigation. The dry alginate dissolves slowly in water; at a concentration of 0.7%, a viscous solution is obtained which rats drink readily from a standard drinking spout. Rats of this weight group drink approximately 20 ml. per day, and therefore imbibe about 140 mg. alginate.

To give higher doses of alginate, the powder is mixed with a smaller amount of water. The alginate swells considerably on wetting, and at a concentration of 5 g. % forms a stiff, pasty gel which can be mixed with lab. chow. Even at high concentrations the rats eat this mixture with great relish. A total of 240 rats kept continuously on such a diet for several weeks developed no evidence of constipation or other untoward symptoms.

Animals fed on the chow-alginate diet ingested enough water in their food to satisfy their thirst. No drinking water was required. In order to ensure that control rats consumed a similar quantity of water, boiled corn-starch paste of a similar concentration was mixed with the chow. This procedure also facilitated the incorporation of Sr^{89} into the feed.

Measurement of Absorption of Radioactive Elements

Bone uptake of radioisotope in the femur was taken as assessment of absorption in these experiments. This is probably strictly true only in the case of strontium which is not concentrated in other tissues.

At the end of each experiment the animals were sacrificed and one whole femur from each animal was dissolved in concentrated HCl. Aliquots of neutralized solution were assayed for radioactivity as described previously.[1, 2]

EFFECT OF VARYING CONCENTRATIONS OF SODIUM ALGINATE ON THE ABSORPTION OF SR^{89} AND CA^{45}

Sodium alginate in the proportions 3, 6, 12, 18 and 24% was mixed with lab. chow as described above and fed to groups of 12 rats in each case. Sr^{89}, 0.5 μc. per g. lab. chow, was included at the same time. At the end of 24 hours, the food mixture had been completely consumed; it was calculated that each rat had ingested on an average 10 g. chow, 5 μc. Sr^{89} and 0.3-2.4 g. alginate. An equal number of rats were fed with a starch-chow-Sr^{89} mixture. These diets were continued for two days. After this time, the chow mixtures were replaced by standard chow for a further 24 hours, when the animals were sacrificed. The 24-hour interval was allowed to elapse, as it was found from previous work[2] that the bone uptake of Sr^{89} reached a steadier state in this interval.

Increasing the amount of alginate in the diet effected a progressive reduction of Sr^{89} uptake in the femur (Table I). The mean radioactive count after the ingestion of 0.3 g. sodium alginate per day was two-thirds that in the controls. By increasing the intake to 2.4 g. per day, uptake of Sr^{89} in the femur was reduced to approximately one-third (31%) of the controls (Fig. 1). Larger amounts of alginate in the diet (3.6 g. and 4.8 g. per day) were also given in an attempt to reduce Sr^{89} absorption even further. The volume of chow mixture became so large, however, that the rats did not consume their prescribed dose of alginate or Sr^{89} in the two-day period.

In the parallel experiments with 0.5 μc. Ca^{45} per gram chow, sodium alginate at the rate of 0.3 g. per day had no effect on bone uptake. When the dose of alginate is increased, some reduction in Ca^{45} uptake is observed, reaching 65% of the control value at a dosage of 2.4 g. per day. Sodium alginate therefore extends the physiological discrimination against strontium by binding it more effectively than calcium. The physiological discrimination is

TABLE I.—EFFECT OF INCREASING CONCENTRATIONS OF SODIUM ALGINATE ON CA^{45} AND SR^{89} UPTAKE
Diet contained 0.5 μc. Sr^{89} or Ca^{45} per g. standard laboratory chow with varying amounts of alginate in jelly form

	Control	*3% alginate*	*6% alginate*	*12% alginate*	*18% alginate*	*24% alginate*
Strontium-89	21,185 (±4,250)	13,781 (± 2,905)	13,088 (± 1,986)	9609 (± 1,805)	8,054 (± 1,449)	6,660 (± 1,505)
% $\frac{\text{Expt.}}{\text{Control}}$		65	62	45	38	31
Calcium-45	65,454 (±22,394)	66,054 (±10,116)	58,129 (±11,293)	53,637 (±16,026)	42,791 (±11,366)	42,770 (± 8,946)
% $\frac{\text{Expt.}}{\text{Control}}$		101	89	82	65	65
Observed ratio	0.32	0.22	0.22	0.17	0.18	0.15

Each figure represents mean counts per minute (femur) and standard deviation of studies in 12 animals.

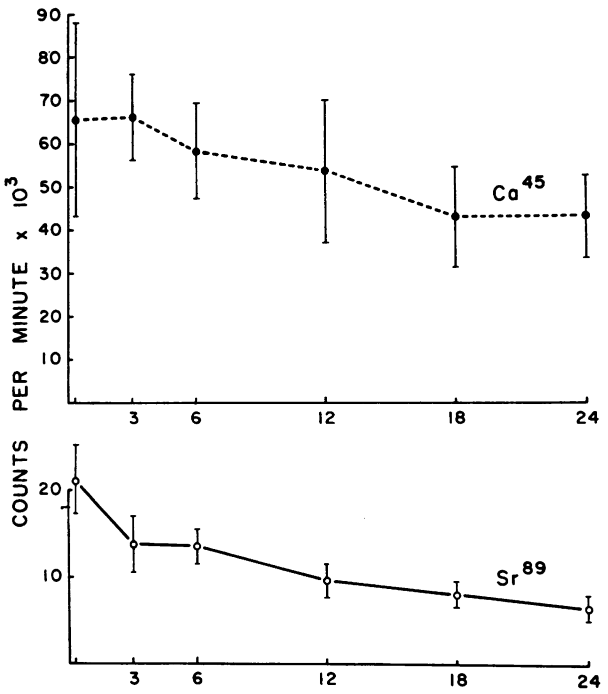

Fig. 1.—Effect on Sr^{89} and Ca^{45} bone uptake of adding increasing amounts of sodium alginate. The alginate was mixed as a jelly with standard laboratory chow.

evaluated by the term:

$$\frac{Sr^{89}/Ca^{45}\text{ bone}}{Sr^{89}/Ca^{45}\text{ diet}}$$

(Comar, Wasserman and Nold[3]), designated the *Observed Ratio or OR.* The OR for the control series in these experiments over a period of two days was found to be 0.32, whereas the OR for rats on a diet of 2.4 g. alginate per day was decreased to 0.15.

Continuous Administration of High Levels of Sr^{89}

(Sodium Alginate Mixed with Food)

Rats were fed on a diet containing 0.5 μc. Sr^{89} and 0.24 g. sodium alginate per gram chow, *ad libitum*, for 20 days. Groups of 12 rats were sacrificed at two, five, 10, 15 and 20 days. An equal number of rats in the control series fed on starch—0.5 μc. Sr^{89}/g. chow diet were treated in the same way.

The results are given in Table II. Sr^{89} uptake in the femur increases steadily in the controls,

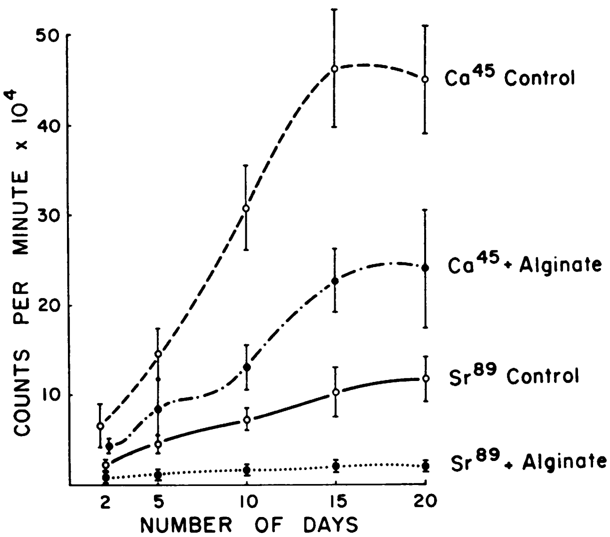

Fig. 2.—Effect of continuous feeding of sodium alginate jelly mixed with diet on Sr^{89} and Ca^{45} uptake in the femur.

whereas the rate of uptake with alginate is much lower (Fig. 2), reaching a steady-state plateau after 15 days. As would be expected, the uptake of Ca^{45} in the bone is much more rapid than Sr^{89}. A plateau or equilibrium state is reached after 15 days. Ca^{45} absorption is reduced by this high level of alginate but to a much lower degree than with Sr^{89}, so that after 20 days the "Observed Ratio" of discrimination against Sr^{89} is reduced to 0.08.

Continuous Administration of Low Levels of Sr^{89}

(Sodium Alginate Supplied in the Drinking Water)

Rats were fed on standard Purina chow *ad libitum* but their drinking water was replaced by a solution containing 0.7 g. sodium alginate and 1.0 μc. Sr^{89} per 100 ml. The average daily intake of Sr^{89} therefore was 0.2 μc. with 140 mg. sodium alginate. Groups of six rats were sacrificed after 24 hours, five days, 10, 15 and 20 days. Similar groups of rats drinking pure water containing 0.01 μc. Sr^{89} per ml. were taken as controls. One femur was taken from each rat for Sr^{89} assay. A parallel series with Ca^{45} was treated under identical conditions.

The results are given in Table III. Sodium alginate given at the rate of 0.14 g. per day had an

TABLE II.—Effect of Continuous Feeding with Sodium Alginate on Sr^{89} and Ca^{45} Uptake
Diet containing 0.5 μc. Sr^{89} or Ca^{45} plus 0.24 g. sodium alginate as a jelly per gram chow.

	Strontium-89			*Calcium-45*			*Observed ratio*	
No. of days	*Control*	*With 24% alginate*	*Expt./control* %	*Control*	*With 24% alginate*	*Expt./control* %	*Control*	*with 24% alginate*
2 days	21,185 (± 4,250)	6,660 (± 1,505)	31	65,454 (±23,396)	42,770 (± 8,946)	65	0.32	0.15
5 days	44,605 (±11,621)	10,297 (± 2,730)	23	145,350 (±27,238)	84,950 (±35,587)	58	0.30	0.12
10 days	72,219 (±14,166)	15,073 (± 2,013)	21	308,227 (±52,389)	131,714 (±24,905)	43	0.23	0.11
15 days	102,129 (±29,492)	20,804 (± 3,880)	20	462,504 (±63,043)	226,659 (±35,690)	49	0.22	0.09
20 days	117,776 (±24,735)	20,078 (± 3,081)	17	451,325 (±62,568)	239,045 (±64,683)	53	0.26	0.08

Each figure represents mean counts per minute (femur) and standard deviation of studies in 12 animals.

TABLE III.—EFFECT OF CONTINUOUS ADMINISTRATION OF SODIUM ALGINATE IN DRINKING WATER ON Sr^{89} AND Ca^{45} UPTAKE
The drinking water contained 0.01 μc. Sr^{89} or Ca^{45} with 7 mg. sodium alginate per ml.

	Strontium-89			*Calcium-45*			*Observed ratio*	
No. of days	*Control**	*Experiment**	*Expt./control* %	*Control**	*Experiment**	*Expt./control* %	*Control*	*Experiment*
1 days	785 (±184)	750 (±212)	95	2,541 (±824)	2,216 (±172)	87	0.30	0.33
5 days	2,971 (±546)	2,191 (±366)	74	7,950 (±1,812)	8,010 (±2,903)	100	0.37	0.27
10 days	5,270 (±1,073)	4,031 (±651)	76	14,850 (±2,850)	13,433 (±1,888)	90	0.35	0.30
15 days	6,194 (±3,017)	4,586 (±1,622)	74	26,108 (±1,644)	27,230 (±4,800)	104	0.23	0.16
20 days	8,421 (±1,567)	4,307 (±1,293)	51	26,660 (±4,617)	27,980 (±6,654)	97	0.31	0.16

*Each figure represents mean counts per minute (femur) and standard deviation for studies in six animals.

appreciable effect (75% controls) on reducing Sr^{89} uptake after five days. The curves defining uptake at first diverge slowly from the control (Fig. 3). After 20 days, however, the differences increased; absorption of Sr^{89} was decreased to 51% of the controls.

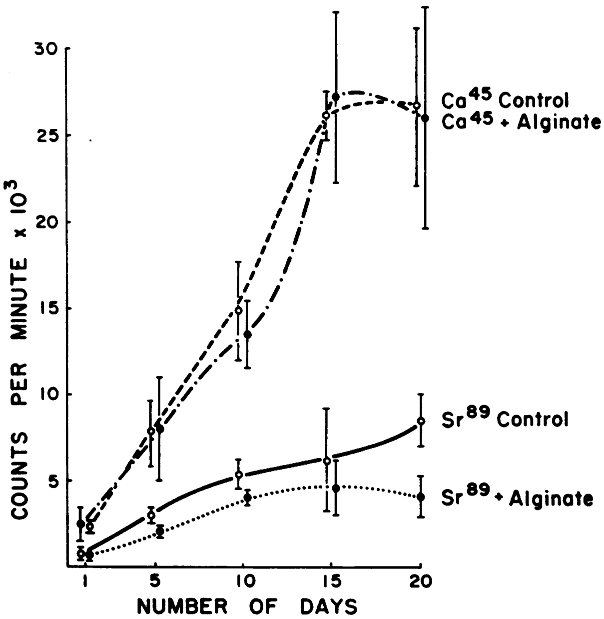

Fig. 3.—Effect of continuous administration of sodium alginate in the drinking water on Sr^{89} and Ca^{45} uptake in the femur.

The curve of uptake of Ca^{45} in the presence of such small quantities of alginate almost coincides with the controls. No interference with calcium intake is therefore to be expected.

DISCUSSION

The results of the feeding experiments described in this paper confirm and extend our earlier conclusions, from studies using ligated intestinal segments and intubation, that sodium alginate is an effective agent for reducing Sr^{89} absorption in rats.[1, 2] Our investigations in a larger series of feeding experiments, to be reported elsewhere, have shown that Sr^{89} uptake by the femur is directly proportional to the amount of radioactive isotope administered. Uptake is also proportional to the length of time for which it is given, although equilibrium appears to be reached by the 20th day. Adequate dosages of sodium alginate suppress bone uptake in every case to an apparent minimum of 17% of the corresponding controls in the long-term experiments. The relationship between dosage of alginate and bone uptake of Sr^{89} is not so direct; by increasing the intake of alginate eight-fold (from 3 to 24%) in the short-term experiments, absorption and bone uptake is decreased by a factor of two.

Sodium alginate shares with another polyuronic acid, polygalacturonic acid (from fruit pectin), the ability to precipitate with alkaline earth metals (except Mg). Sulfated polysaccharides such as carrageenin do not have this property. Preliminary experiments with sodium polygalacturonate[4] indicate that it is equally efficacious in suppressing Sr^{89} absorption. Since these experiments were carried out, it was brought to our attention that both sodium alginate and pectin (the methyl ester of polygalacturonic acid) were tested by MacDonald *et al.*[5] in 1952. Their experiments differed in that they measured the skeletal uptake of non-radioactive strontium after administration of relatively massive doses of strontium chloride. They found that pectin decreased strontium accumulation in the bones but failed to detect activity with alginate. This failure was probably due to the very small amount of alginate in solution which they were able to give; sodium alginate forms a very viscous solution and at high concentrations cannot be given by orogastric tube. On the other hand, pectin is more water soluble and their dose was 10 times as high.

The polyuronic acids are similar in their activity of suppressing strontium absorption to the ion exchange resins.[4] However, as has been pointed out,[6] there are many disadvantages in maintaining a long-term diet of synthetic resins. Firstly, these materials are unpalatable, especially when taken in bulk; secondly, the speed of food transit through the digestive tract is markedly reduced; thirdly, the efficiency of treatment decreased with time. McChesney and McAuliff[7] found that although treatment with ion-exchange resins altered the mineral balance of rats, no deleterious effects were observed. However, the advisability of maintaining humans on synthetic resins for long periods has, in general, been in question, as symptoms of K^+ deficiency have been reported in certain conditions.[8]

Sodium alginate appears to suffer from none of these disadvantages. It is palatable in solution or as a jelly; no untoward symptoms were observed in rats fed continuously on high concentrations of alginate for many weeks. It does not bind the alkali metals, while at low dosages there is no reduction in calcium absorption. At very high dosages, Ca^{45} deposition is reduced to some extent. After 20 days, however, rats maintained on this diet showed no clinical evidence of calcium deficiency; growth rate was the same as in control groups on standard chow.

Sodium alginate dissolved in water appears to cause no gastrointestinal disturbances. In earlier experiments in which dry alginate was mixed with the diet, severe constipation developed. This may be explained by the nature of alginate, which swells considerably on mixing with water, forming concretions in the stomach where acid tends to harden the mass. Lumps of swollen alginate probably become the nucleus of hard fecal masses and are the direct cause of constipation.

SUMMARY AND CONCLUSIONS

The results obtained in the foregoing experiments indicate that, under laboratory conditions, sodium alginate effectively reduces Sr^{89} uptake (by up to 83%) following feeding of the binding agent mixed with the diet. The fact that administration of sodium alginate in a jelly form overcomes the problem of constipation represents a significant finding with respect to the use of the compound in human subjects. The alginate swells considerably on wetting and at a concentration of 5 g. % forms a stiff, pasty gel which can be mixed with the food. Addition of sodium alginate to drinking water is effective with low levels of Sr^{89} intake.

Increasing the amount of alginate in the diet caused a progressive reduction of Sr^{89} in the femur. Long-term experiments were also carried out in which two different levels of radioactivity were given to determine the pattern of Sr^{89} deposition with continuous intake of the binding agent. A parallel series of experiments using Ca^{45} was performed in order to detect calcium deficiency. At very high dosage, Ca^{45} deposition is reduced to some extent, but no clinical evidence of calcium deficiency was observed.

It may be possible to extend the use of naturally occurring, water-soluble macromolecular substances to bind other divalent cations or toxic products. The fact that these polymers are not absorbed offers the possibility of preventing intestinal absorption of undesirable substances from food or drinking supplies, by simultaneous ingestion of binding agent; this field warrants further investigation. The acidic polysaccharides described in this work have several advantages compared with synthetic ion-exchange resins, with respect to palatability and the development of imbalances of Na and K.

The technical assistance of Mr. Michael Farrell, Mr. Serge Podymov and Miss Margaret Evans is gratefully acknowledged.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE BLACK HOLE OF CALCUTTA

The prisoners were gathered on the piazza and at night were driven into a room about eighteen feet square and twelve feet high, one hundred and forty-five men and one woman, the soldiers could barely pack the last man in. There were two iron-barred windows and they were on the side away from the prevailing wind. Inside the room was a platform about six feet wide and four feet high. The men were placed in this room at eight o'clock in the evening on a close sultry night, even for Bengal, and when released at six o'clock next morning only twenty-three had survived. Holwell was the first to enter and went straight to one of the windows. Before nine o'clock (one hour) the occupants were in a desperate state—profuse perspiration and raging thirst. They removed their clothes, this gave them relief for a moment, they waved their hats thinking to produce a current of air, they tried squatting down so that they would have more air above and possibly more breathing space. During this experiment many were so weak that they were unable to rise again and were trampled to death or suffocated. During the second hour the thirst became intense, respiration was difficult and some became delirious. Holwell standing by the window now began to feel the same symptoms of thirst and difficult breathing and the atmosphere in the room became charged with 'a strong urinous volatile effluvia' and there was a constant cry for water. Water was conveyed into the room in hats forced through the bars of the windows, but most of it was spilled owing to the crazed state of the men, but even those who got a little found that it did not help much. By eleven o'clock one-third of the occupants of the room were dead. Holwell worked his way from the window where he had been jammed by those behind trying to get at the window for water, and crossing over the dead to the other side of the room lay down on the platform to die.

All this time the guards dared not waken the drunken ruler and it was not until six o'clock the next morning that they reported to him the desperate condition of affairs. He then sent word to open the doors and search for Holwell. After some difficulty (so great was the pressure of bodies against the door) this was done and, after considerable search, Holwell was found on the platform under several bodies in an unconscious condition. When brought before the ruler he could not speak so great was his exhaustion, though he tried to explain that they had no treasure. Holwell mentions that the steam and stench from both the dead and the living bodies was insufferable and that about two a.m. he was sensible of no pain and only a little uneasiness and fell into a stupor.—Medical Societies, *Canad. Med. Ass. J.*, 4: 936, 1914.