Effect of age on heavy metal absorption

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In 1971 a very high absorption of lead was reported after oral administration in suckling rats (Kostial *et al.* 1971*a,b*). Since then several authors have confirmed a high absorption not only of Pb but also of other toxic metals as a specific finding in suckling animals (Forbes & Reina, 1972; Sikov & Mahlum, 1972; Inaba & Lengemann, 1972; Kello & Kostial, 1977*b*; Quarterman & Morrison, 1978; Kostial *et al.* 1978; etc.). Relevant experimental results on humans are scarce, but the few existing results indicate that this finding, especially as far as lead is concerned, might be also relevant for infants (Alexander *et al.* 1974; Ziegler *et al.* 1978).

The metabolism of toxic metals in sucklings is not only characterized by a greatly increased intestinal absorption but also by a different organ distribution. The most striking differences were observed in the brain where suckling animals retained a much higher fraction of Pb, manganese and mercury than adult animals (Kostial *et al.* 1978). The evidence obtained in experimental animals and humans indicates that the perinatal age also might be a period of increased susceptibility of the central nervous system to toxic metals (Nordberg *et al.* 1978).

On the basis of these findings it is now generally accepted that age might be an important factor in determining the metabolism and health effects of toxic metals. However, several aspects in the metabolism of toxic metals in neonates are still uncertain. This specially applies to factors accounting for a greatly increased intestinal absorption at this age. For some metals, like Pb, the increased body retention in sucklings after an oral dose was found to be entirely related to the retention in the gut-free carcass (Kostial *et al.* 1971*a,b*). The increased body retention of cadmium, however, was mainly related to a higher gut retention, which was maintained in neonates for a considerable period of time after oral administration (Sasser & Jarboe, 1977; Kostial, Kello *et al.* 1979). During this period a high oral toxicity of some metals, especially of Cd, was also observed in suckling rats (Kostial *et al.* 1978; Kostial, Kello *et al.* 1979). An increased and prolonged gut retention in the neonates was also observed for ^{141}Ce (Inaba & Lengemann, 1972) and ^{95}Nb (Mraz & Eisele, 1977).

Additional experimental evidence on absorption and distribution of Cd and Hg in sucklings

All experiments were performed on suckling rats. Litters were reduced to six animals each. Sucklings were kept in individual cages with their mothers, and had free access to mother's food until the age of three weeks when they were transferred to plastic cages and received only stock diet and water *ad lib.* At 6 d of age pups were divided into two groups of eighteen litters each: the first group

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Table 1. *Retention of ^{115m}cadmium and ^{203}mercury in suckling rats (% dose) after oral and intraperitoneal administration*

(Values are arithmetic means with their standard errors. No. of rats in parentheses)

Radio-isotope	Period after administration (d)		Gut Mean	Gut SE	Liver Mean	Liver SE	Kidneys Mean	Kidneys SE	Carcass Mean	Carcass SE	Whole Body* Mean	Whole Body* SE	Apparent† absorption Mean	Apparent† absorption SE
^{115m}Cd	7	(11)	11·24	0·85	5·32	0·62	0·43	0·04	3·32	0·29	20·32	0·99	9·07	0·87
(oral)	14	(10)	2·60	0·25	6·02	0·63	0·52	0·04	3·30	0·45	12·42	1·17	9·84	1·02
	21	(9)	0·96	0·08	4·97	0·35	0·62	0·03	2·43	0·18	8·98	0·48	8·02	0·44
^{115m}Cd	7	(9)	9·85	0·45	36·52	1·14	2·07	0·08	36·22	1·77	84·67	2·29	74·81	2·34
(intraperitoneal)	14	(18)	5·52	0·39	34·62	1·37	3·03	0·12	32·83	1·30	75·99	2·49	70·47	2·40
	21	(9)	2·50	0·20	28·80	1·49	4·70	0·28	36·08	1·35	72·07	2·58	69·58	2·54
^{203}Hg	7	(18)	54·08	1·76	3·12	0·14	1·99	0·12	8·26	0·35	67·46	2·16	13·38	0·54
(oral)	14	(18)	5·00	0·58	4·59	0·25	4·04	0·25	9·96	0·63	23·59	1·36	18·59	1·04
	21	(18)	1·03	0·08	2·39	0·24	5·24	0·37	6·86	0·54	15·52	1·16	14·49	1·08
^{203}Hg	7	(9)	5·57	0·23	15·65	1·11	15·90	0·89	50·21	1·35	87·33	2·74	81·76	2·61
(intraperitoneal)	14	(9)	4·91	0·67	14·98	0·89	20·03	1·08	35·06	1·27	74·99	2·87	70·08	2·79
	21	(9)	3·16	0·16	6·57	0·55	22·02	0·56	24·95	0·34	56·71	0·95	53·55	0·88

*Sum of gut, liver, kidneys and carcass retention.
†Sum of liver, kidneys and carcass retention.

received radioactive Cd and the second radioactive Hg (fifty-four sucklings by oral and fifty-four by intraperitoneal administration of ^{115m}Cd and ^{203}Hg respectively). From each litter one or two animals were killed every week, i.e. 7, 14 and 21 d after the radioisotope administration. The animals left over from some litters were used for other purposes. After dissection the intestinal tract distal to the diaphragm (including contents), the liver and both kidneys were removed from the carcass, blotted free of blood and placed in appropriate containers for radioactivity determination. Both radioactive isotopes were administered in the form of chlorides and were supplied by the Radiochemical Centre, Amersham, with a specific activity of 0·24 μCi/μg ^{115m}Cd and 1·7 μCi/μg ^{203}Hg. For oral administration the artificial feeding method was used (Kostial *et al.* 1967). Each animal received about 20 μCi of ^{115m}Cd or 3 μCi of ^{203}Hg in about 0·5 ml of cow's milk by means of a dropper over 6–7 h. Intraperitoneally the rats received about 10 μCi of ^{115m}Cd or 2 μCi of ^{203}Hg in a volume of 0·02 ml. The radioactivity was determined in the gastrointestinal tract (G), liver (L), and both kidneys (K) by means of a well type automatic gamma counter (Nuclear Chicago), and in the carcass (C, whole body after removal of G, L and K) by means of a whole body detector equipped with two scintillation crystals (Tobor, Nuclear Chicago). Tissues were assayed for sufficient time that the counting error was less than 3%. The results were corrected for radioactive decay and sample geometry and are expressed as the percentage of the administered dose. The whole body (WB) retentions were calculated as the sum of all the measured values (G, L, K, C), and the apparent absorption (A) as the sum of the measured retention values without the gastrointestinal tract (L, K, C).

The results in Table 1 show a steep parallel decrease in the whole body and gut retention between the first and second time interval after oral administration of ^{115m}Cd and ^{203}Hg, indicating that the high percentage of the whole body radioactivity retained 7 d after radioisotope administration was mainly related to gut retention. In the gut compartment most of the Cd and Hg was eliminated from the body after the first time interval and only a smaller fraction entered into other body compartments. In Fig. 1 all values are presented as percentages of the apparent absorption in the first time interval after ^{115m}Cd and ^{203}Hg administration. In this way differences in Cd and Hg retention in the body and organs after oral and intraperitoneal administration are better demonstrated. Between the first and second time interval most retention values increased after oral administration of ^{115m}Cd and ^{203}Hg or decreased less than after intraperitoneal administration. This is more pronounced for ^{203}Hg than for ^{115m}Cd retention indicating that a fraction of Cd and especially of Hg from the gut compartment represents a source of additional body burdening to other organs. Sucklings retain a much higher fraction of an oral dose of ^{115m}Cd and ^{203}Hg in the whole body than older rats which under similar experimental conditions retain only about 1% of these radioisotopes (Kostial *et al.* 1978). In older animals only a small fraction of the whole body radioactivity was retained in the gut (Kostial, Kello *et al.* 1979; Kostial, Rabar *et al.* 1979). Sucklings also retain a higher percentage of an

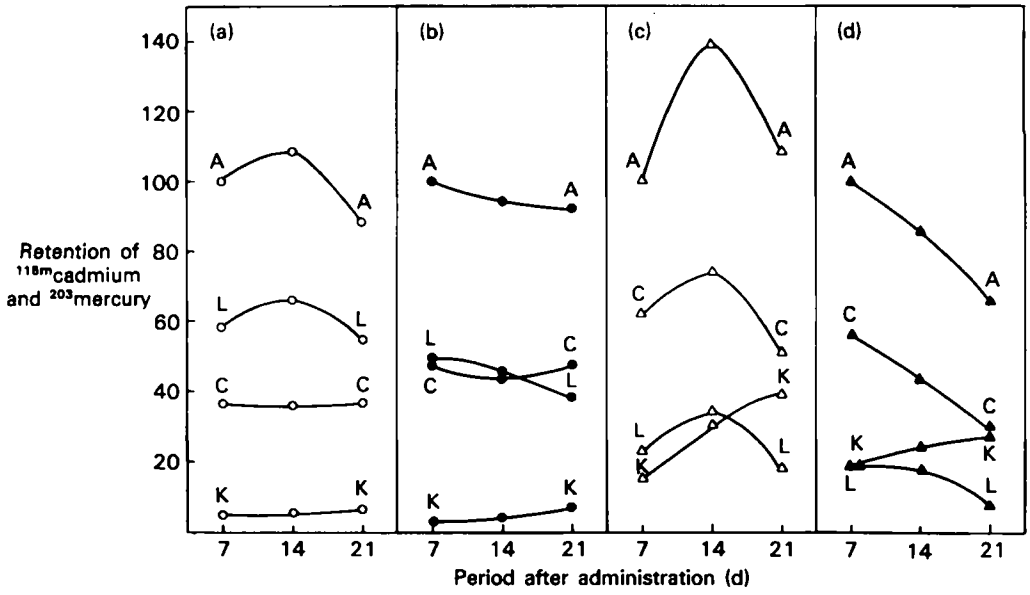

Fig. 1. Retention of ^{115m}cadmium and ^{203}mercury in liver (L), kidneys (K), carcass (C), and the apparent absorption (A) 7, 14 and 21 d after administration of radioisotopes to 6 d old suckling rats. Results are expressed as percentages of A 7 d after administration of: (a) oral ^{115m}Cd, (○—○); (b) intraperitoneal ^{115m}Cd, (●—●); (c) oral ^{203}Hg, (△—△); (d) intraperitoneal ^{203}Hg, (▲—▲). Values are presented as arithmetic means of nine–eighteen rats in each group.

intraperitoneal dose of ^{115m}Cd and ^{203}Hg and show different organ distribution which is in agreement with our previous results and has been already discussed in detail (Kello & Kostial, 1977*a*; Kostial *et al.* 1978; Kostial, Kello *et al.* 1979).

Discussion and conclusions

The results of the experiments reported here indicate that for some toxic metals, like Cd or Hg, the gut compartment should not be neglected when estimating the intestinal absorption in sucklings. This compartment, if determined at later time intervals after administration, does not represent the unabsorbed or endogenous fraction, but the fraction of the metal incorporated in the gut. A part of this fraction by being transferred to other parts of the body also increases the already high body burden of these metals in other organs. The significance of the high gut retention and longer residence time of some metals in sucklings is still uncertain. There is some evidence of depressed intestinal activity (Hietanen, 1978; Sasser & Jarboe, 1977), citotoxicity (Koo *et al.* 1978) and entheropathies (Richardson & Fox, 1974) in experimental animals after oral exposure to Cd. Histological abnormalities of the intestinal mucosa were observed in patients with the Itai-itai disease (Muto & Omori, 1977). A very high oral toxicity of some metals especially of Cd in neonatal rats might be also related to higher gut retention and not only to increased absorption (Kostial *et al.* 1978; Kostial, Kello *et al.* 1979).

Little is known about the mechanism of metal absorption in general and even less is known about this mechanism in sucklings. Based on some of our previous

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and present results, we shall try to consider a few facts about the cation absorption in neonates. The neonatal age is a period in which no differences in the intestinal absorption between cations with and without an active transport mechanism have been observed (the same percentage of strontium and calcium is absorbed in sucklings while about three times less Sr than Ca is absorbed in older rats, Kostial *et al.* 1967). This is also a period in which the absorption of homoeostatically controlled cations like Ca is different from that in adults (in suckling rats fed on milk with a seven times higher concentration of Ca the retention of an oral dose of radioactive Ca does not decrease as in older animals, Kostial *et al.* 1967; Kostial *et al.* 1969). At this age the competitive mechanism of cation absorption also seems to be different from that in adults (a high increase in the iron concentration of milk fails to reduce ^{115m}Cd and ^{203}Hg absorption in suckling rats in contrast to adult animals (Kostial, Rabar *et al.* 1979). It is a period when some metals have a higher retention and longer residence time in the gut of sucklings than in adults.

Most of these specific features in cation absorption last only until weaning, when structural and functional changes occur in the gut and when sucklings change from milk diet to very different dietary conditions. The relative importance of these factors on drastic changes in absorption, gut retention and toxicity are not yet clear. Milk diet is known to enhance the absorption of several metals in older rats (Kello & Kostial, 1973; Kello & Kostial, 1977*b*; Kostial *et al.* 1978), and this might be related to a relatively low concentration of several essential elements in milk. The importance of dietary factors in general and especially of minerals in the metabolism and health effects of metals is an important new topic in recent investigations (Mahaffey, 1974; Klauder & Petering, 1975; Petering, 1978; Jacobs *et al.* 1978; Bremner & Campbell, 1978; Quarterman *et al.* 1978; Fox, 1978).

These and several other factors contribute to the high absorption of metals in sucklings, which might cause a higher body burden of metals at an age when this is highly undesirable.

The present results are in agreement with our previous findings of a greatly increased absorption of toxic metals in neonates. The high intestinal absorption with or without a simultaneous higher retention and longer residence time in the gut is a specific feature of metal absorption in neonates and most probably applies to toxic as well as to essential elements. However, for toxic metals this finding might be very relevant for estimating the potential health effect, since the neonatal age is a critical period for metal accumulation and toxicity.

The high absorption of metals in sucklings and our insufficient knowledge of the mechanism of metal absorption in relation to age and diet is a problem of serious concern in setting up limits for toxic metal exposure in the youngest age group.

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