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THE recent development of quantitative co-ordination chemistry is paralleled by remarkable advances in the therapeutic use of chelating agents, for example, in the removal of toxic or radioactive metals from the body.

In the particular case of radiocobalt, however, our knowledge about the efficacy of chelators is rather scanty: ethylenediamine-tetraacetic acid (EDTA)[1–5], diamino-*cyclo*hexanetetraacetic acid[6], diethylenetriaminepenta-acetic acid (DTPA)[2], cysteine (Cy)[4,5] and cysteamine (CyA)[4,5] have been tested and found to be effective, DTPA being slightly superior to the other compounds.

In order to find chelators with still higher efficacy, one must take into account the fact that Co(II) is a transition metal. With regard to co-ordination properties, the transition metal ions are known to behave quite individually and to react not only with oxygen as ligand atom, but also with nitrogen and sulphur. Therefore, screening tests with a greater number of corresponding chelators were necessary.

Albino rats of the Heiligenberg strain (6–10 weeks old, 170–210 g) were intravenously injected with approximately 5 μc. of carrier-free $^{60}CoCl_2$. To achieve maximum effectiveness, the different compounds were administered immediately after the injection of ^{60}Co. The dosage was 200 μmoles per animal, with the exception of the relatively toxic 2-mercapto-ethyliminodiacetic acid (MEIDA) (25 μmoles). The animals were killed 48 h later, and the radioactivity of the organs assayed by means of a KI(Tl)-scintillation crystal.

In good agreement with earlier investigations, ^{60}Co was eliminated rather quickly from the body, and the total retention after 48 h amounts to 8–11 per cent. The highest concentrations are observed in liver and kidneys. As can be seen from Table 1, our data confirm the findings of Foreman[2], that is, the superiority of DTPA over EDTA. This accords with the ratios of the relevant stability constants $K^{Co}_{CoL}/K^{Ca}_{CaL}$: $10^{8.4}$ for DTPA[7] and $10^{5.5}$ for EDTA[8]. DTPA does not occupy, however, the same unique position as it does with other metal ions[9], and its efficacy is equalled by triethylenetetramine-hexaacetic acid (TTHA), 2 : 2′-*bis*[di(carboxymethyl)-amino]diethyl ether (BADE), 1 : 2-*bis*[di(carboxymethyl)-aminoethoxy]ethane (BAE), MEIDA, Cy and CyA and clearly surpassed by the sulphur-containing 2 : 2′-*bis*-[di(carboxymethyl)amino]diethyl sulphide (BADS), 1 : 2-

Table 1. ^{60}Co-CONTENT (MEANS OF 5–6 RATS AND STANDARD ERRORS) IN DIFFERENT ORGANS 48 H AFTER INJECTION

The chelating agents (with the exception of DMCy, Cy and CyA, given as Ca-Na-chelates) were administered intraperitoneally, immediately following the injection of the radionuclide

Chelate	Percentage recovery of ^{60}Co dose in:			
	Kidneys	Liver	Muscle	Bones
Control	0·836 ± 0·014	4·857 ± 0·148	2·137 ± 0·034	0·585 ± 0·017
EDTA	0·959 ± 0·049	2·605 ± 0·110	1·453 ± 0·083	0·370 ± 0·014
DTPA	1·197 ± 0·018	1·830 ± 0·046	0·875 ± 0·059	0·106 ± 0·004
TTHA	0·965 ± 0·047	1·150 ± 0·027	1·225 ± 0·031	0·154 ± 0·004
BADE	0·436 ± 0·019	2·108 ± 0·053	0·748 ± 0·035	0·202 ± 0·005
BAE	0·581 ± 0·014	3·684 ± 0·124	1·616 ± 0·075	0·377 ± 0·008
BADS	0 204 ± 0·005	0·408 ± 0·005	0·647 ± 0·026	0·075 ± 0·005
BATE	0·155 ± 0·004	0·763 ± 0·021	0·613 ± 0·041	0·077 ± 0·002
Cy	0·385 ± 0·005	1·774 ± 0·038	1.112 ± 0·038	0·303 ± 0·011
CyA	0·734 ± 0·014	1·701 ± 0·057	1·017 ± 0·033	0·313 ± 0·006
DMCy	0·200 ± 0·025	0·858 ± 0·113	0·730 ± 0·052	0·260 ± 0·034
DMCy*	0·151 ± 0·005	0·576 ± 0·026	0·592 ± 0·016	0·138 ± 0·008
MEIDA†	0·268 ± 0·022	2·228 ± 0·219	1·070 ± 0·096	0·441 ± 0·042

* The dose of 20 μmoles DMCy was given orally.

† The MEIDA contains ~10 per cent of cystaminetetraacetic acid as impurity.

bis[di(carboxymethyl)aminoethylthio]ethane (BATE) and D-β,β′-dimethylcysteine (DMCy). Although the participation of the sulphur atoms in chelating Co(II) is beyond doubt, it is not yet clear (since the K^{Co}_{CoL}-values are not available) whether the high efficacy of the sulphur compounds is due only to their low K^{Ca}_{CaL}-values or also to high K^{Co}_{CoL}-values.

The chelators show different patterns of effectiveness, that is, the differences in effectiveness are more pronounced in relation to the kidney than in other organs: EDTA, DTPA, TTHA, CyA are not able to reduce the retention of ^{60}Co by the kidney, whereas the other compounds were found to be markedly effective. The reasons for this discrepancy are not yet fully understood. Tentatively, different metabolic behaviour of particular chelates as well as the formation of ternary complexes in the kidneys (which are known to possess a high concentration of SH-groups[10]) can be assumed.

From the practical point of view the therapeutic use of BADS and BATE in cases of internal contamination with ^{60}Co is obvious. However, the highest significance must be attributed to D-dimethylcysteine (commonly known as penicillamine). Its high efficacy compares favourably with BADS and BATE. Our experimental data show that it can be administered orally without

loss of effectiveness: Finally, its low toxicity must be stressed. More detailed studies on the effectiveness of these and other chelators, as influenced by several factors and, in particular, the time of their administration, are now under way and will be published elsewhere.

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