(Table). Neither the α nor β antagonists injected by themselves affected feeding when compared to that of the controls.

Abdominal temperatures were not significantly affected by any of the treatments. This is unlike the response of other species which when injected with prostaglandins have shown hyperthermia[2,4]. In most cases, including controls, there appeared to be a slight elevation in temperatures during the 15 min prior to injection. This change was probably due to the handling of the animals.

After sacrificing the sheep, the injection loci were located in the anterior hypothalamus at 28, 29 and 30 mm anterior of the external auditory canal according to the coordinates of RICHARD[14].

In the present experiment we have shown as in a previous experiment[13] that a β agonist, dl-Isop, injected intrahypothalamically will elicit feeding in sheep with smaller doses (8 nmoles) than those injected into the perifornical region of the hypothalamus of rats which have either no effect[5,7] or cause hypophagia (150 nmoles)[15]. Injections of PGE_1 into these loci also caused marked feeding which was blocked by a specific β antagonist. A prostaglandin antagonist, polyphloretin phosphate, injected at α and β loci by itself also caused significant feeding (BAILE and MARTIN, manuscript in preparation).

The feeding effect produced by PGE_1 at the β loci was similar to that of dl-Isop. This could be a β adrenoceptor effect. A model of a β receptor for PGE_1 has been presented[16] and it was suggested that the 'receptor modulating substance'[17,18] is either a prostaglandin or a substance promoting the synthesis of prostaglandin. PGE_1 and E_2 appear to mimic some of the actions of the β agonist, isoproterenol: both have been shown to stimulate the short circuit current of frog skin[19]; both have a bronchodilator effect[20,21]; both decrease (PGE_2 and dl-Isop) filterability of red blood cells of man, rat and mouse[22] while the Ca^{++} influx is increased. These effects are known to be associated with activation of adenyl cyclase[22,23] a probable link in some β adrenoceptor actions[24]. Whether the feeding effect in sheep following PGE_1 injection at β loci is related to changes in adenyl cyclase level has not been shown.

Depending upon characteristics of the loci tested, PG E_1 either caused no change in feeding or increased feeding (α or β adrenoceptor loci, respectively), but the physiological role in either control of feed intake or regulation of energy balance remain to be shown.

Résumé. Une augmentation de la prise de nourriture a lieu après injection intrahypothalamique du PGE_1, en dose de 21 nmoles, chez les brebis. La température de la cavité abdominale n'est pas affectée par ces injections, sauf une légère augmentation au moment de l'injection et qui peut provenir du maniement des animaux.

F. H. MARTIN and C. A. BAILE[25,26]

University of Pennsylvania and Smith Kline and French Laboratories, 1600 Paoli Pike, West Chester (Pennsylvania 19380, USA), 6 December 1972.

[14] P. RICHARD, *Atlas Stereotaxique du Cerveau de Brebis* (Institut National de la Recherche Agronomique, 149, rue de Grenelle, Paris 1967).
[15] S. F. LEIBOWITZ, Nature, Lond. *226*, 963 (1970).
[16] J. R. SMYTHIES, J. theor. Biol. *35*, 93 (1972).
[17] G. KUNOS and M. SZENTIRANYI, Nature, Lond. *217*, 1077 (1968).
[18] M. SZENTIRANYI, G. KUNOS and A. JOHASZ-NAGY, Am. J. Physiol. *218*, 869 (1970).
[19] H. SHIO, J. SHAW and P. RAMWELL, Ann. N. Y. Acad. Sci. *185*, 327 (1971).
[20] R. L. ADOLPHSON, R. G. TOWNLEY, J. Allergy *45*, 119 (1970).
[21] M. E. ROSENTHALE, A. DERVINIS and J. KASSARICH, J. Pharm. exp. Ther. *178*, 541 (1971).
[22] J. E. ALLEN and H. RASMUSSEN, Clin. Res. *19*, 559 (1971).
[23] F. BASTIDE and S. JARD, Proc. 24th Inter. Congr. Physiol. Sci. Washington, D. C. (1968), Abstract 97.
[24] G. A. ROBISON, R. W. BUTCHER and E. W. SUTHERLAND, in *Fundamental Concepts in Drug-Receptor Interaction.* (Eds. J. F. DANIELLI, G. F. MORAN and D. J. TRIGGLE; Academic Press, N. Y. 1970), p. 59.
[25] We are grateful to Dr. JOHN E. PIKE for the gift of PGE_1.
[26] This research was supported in part by a Grant-in-aid of the National Science Foundation, Grant No. GB-28836.

The Effect of Chelating Agents on the Distribution of ^{210}Po in Rats

Since HURSH's observation that 2,3-dimercaptopropanol (BAL) increases the excretion of ^{210}Po and reduces its toxicity[1,2], 2 other substances were demonstrated to affect the behaviour of ^{210}Po in animals: sodium 2,3-dimercaptopropane-1-sulfonate (DMPS)[3,4], i.e. a water-soluble derivative of BAL, and sodium diethyldithiocarbamate (DDC)[5]. The aim of this screening study was to compare the effectiveness of these 2 chelating agents, as well as of D-penicillamine (PA)[6], 2-mercaptopropionylglycine (MPG)[7] and the Na_3Ca-chelate of diethylenetriaminepentaacetate (DTPA). Furthermore, this is the first attempt to influence behaviour of ^{210}Po also by oral treatment.

Adult female albino rats (weighing 170–200 g) were injected i.v. with $\sim$ 0.3 μCi of ^{210}Po in 0.1 *N* HNO_3. Injection solutions were prepared for each group separately and immediately before administration. Chelating agents (1 mmol/kg) were administered 1.5 min after ^{210}Po i.p. or orally. In the latter case rats were deprived of food for 20 h before administration of the compounds. The animals were sacrificed after 48 h by exsanguination in ether narcosis. The α-activity of tissue samples was determined by liquid scintillation counting[8].

The effect of chelates injected i.p. is summarized in Table I. In general, their effectiveness decreases in the order: DMPS > DDC > MPG > PA; DTPA showed hardly any effect. There is a marked diminution of ^{210}Po-retention in blood, spleen and bone and, less, in blood plasma. Retention of ^{210}Po by the kidneys, however, was reduced by DDC only, while with other chelates a substantial fraction of ^{210}Po was transported into but not excreted from the kidneys. It is feasible that the accumulation of ^{210}Po in the liver following administration of DDC might be due to a temporary storage of ^{210}Po in the excretory organ of DDC. When taking into

[1] J. B. HURSH, J. Pharmac. exp. Therap. *103*, 450 (1951).
[2] J. B. HURSH, Proc. Soc. exp. Biol. Med. *79*, 210 (1952).
[3] Unitiol ®, Leningradskii Khimpharmzavod, USSR.
[4] M. G. PETROVNIN, in *Polonii* (Ed. V. A. SANOTSKII; Meditsina, Moskva 1964), p. 179.
[5] R. S. KRIVCHENKOVA, A. P. SAFRONOV in *Polonii* (Ed. V. A. SANOTSKII; Meditsina, Moskva 1964), p. 245.
[6] Metalcaptase ®, by courtesy of Heyl & Co., Berlin.
[7] Thiola ®, by courtesy of Santen Pharm. Co., Osaka, Japan.
[8] A. SEIDEL, V. VOLF, Int. J. appl. Radiat. Isotopes *23*, 1 (1972).

Table I. The effect of i.p. injected chelating agents on the distribution of ^{210}Po

Agent	No. of rats	Percentage of injected ^{210}Po-dose[a]					
		Whole blood[b]	Blood plasma[b]	Liver	Spleen	Skeleton[c]	Kidneys
Control	10	15.8 ± 0.9 (C)	0.77 ± 0.05 (B)	13.5 ± 0.5 (A)	5.0 ± 0.2 (D)	6.6 ± 0.4 (D)	5.0 ± 0.2 (B)
DTPA	6	12.1 ± 0.9 (C)	0.82 ± 0.10 (B)	17.7 ± 1.8 (B-C)	4.6 ± 0.3 (D)	7.1 ± 0.4 (D)	6.0 ± 0.3 (B)
PA	6	5.9 ± 0.2 (B)	0.72 ± 0.05 (B)	15.0 ± 0.7 (A-B)	2.1 ± 0.1 (C)	4.2 ± 0.2 (C)	16.3 ± 0.3 (C)
MPG	5	2.8 ± 0.3 (A)	0.61 ± 0.10 (A-B)	19.3 ± 2.0 (C)	1.1 ± 0.2 (B)	2.1 ± 0.1 (B)	31.4 ± 1.6 (D)
DDC	6	2.1 ± 0.1 (A)	0.51 ± 0.06 (A)	20.1 ± 1.1 (C)	1.1 ± 0.04 (B)	4.1 ± 0.1 (C)	3.1 ± 0.1 (A)
DMPS	6	2.5 ± 0.1 (A)	0.44 ± 0.05 (A)	16.8 ± 0.5 (B-C)	0.39 ± 0.05 (A)	1.0 ± 0.04 (A)	42.5 ± 1.1 (E)

[a] Arithmetic means ± S.E. The agents were classified by DUNCAN's multiple range test[13] in the order of decreasing effectiveness (A > B > C > D > E). Logarithmic transformation of the data was performed to stabilize variance. [b] Total blood and blood plasma were assumed to equal 5 ml/100 g body wt.$^{-1}$ and 55% of the total blood volume, resp. [c] ^{210}PO in 1 femur times 20.

Table II. The effect of oral chelating agents on the distribution of ^{210}Po

Agent	No. of rats	Percentage on injected ^{210}Po-dose[a]						
		Whole blood	Blood plasma	Liver	Spleen	Skeleton	Brain	Kidneys
Control	6	13.4 ± 0.9 (C)	0.54 ± 0.05 (B)	11.5 ± 0.4 (B)	5.4 ± 0.1 (D)	7.1 ± 0.4 (D)	0.099 ± 0.006 (B)	4.9 ± 0.1 (B)
PA	5	8.9 ± 0.3 (B)	0.49 ± 0.04 (B)	9.6 ± 0.5 (A)	4.0 ± 0.2 (C)	6.0 ± 0.2 (C)	0.072 ± 0.003 (B)	8.4 ± 0.4 (C)
MPG	5	8.9 ± 0.9 (B)	0.46 ± 0.05 (B)	9.5 ± 0.5 (A)	3.5 ± 0.1 (B-C)	4.5 ± 0.4 (B)	0.078 ± 0.006 (B)	22.6 ± 0.5 (D)
DDC	5	3.6 ± 0.7 (A)	0.30 ± 0.03 (A)	19.1 ± 1.0 (C)	3.2 ± 0.2 (B)	5.0 ± 0.1 (B)	0.47 ± 0.03 (C)	3.2 ± 0.2 (A)
DMPS	5	3.8 ± 0.4 (A)	0.26 ± 0.02 (A)	10.8 ± 0.7 (A-B)	0.74 ± 0.06 (A)	1.5 ± 0.1 (A)	0.027 ± 0.003 (A)	47.6 ± 0.9 (E)

[a] For explanations see Table I.

account the overall retention of ^{210}Po in blood, liver, spleen, skeleton and kidneys, it is diminished only after treatment with DDC (by about 35%) while it is increased with MPG (by 25%) and even more with DMPS (by 40%).

The effect of the chelates given orally is presented in Table II. Distribution of ^{210}Po was influenced in a similar pattern as following i.p. treatment, but the effectiveness was less pronounced. The effect of oral DMPS and DDC corresponds to approximately $^1/_3$ of the i.p. dosage, as judged from the dose-effect curves obtained in the latter case[9]. In the liver, however, ^{210}Po decreased after the oral administration of MPG and PA. The striking 5fold increase in the deposition of ^{210}Po in brain due to DDC (observed also after its injection[5]) might be in some relation to the affinity of DDC to this organ[10]. The estimated overall retention of ^{210}Po decreased with DDC and PA (by about 15%), while it increased with MPG (by 15%) and especially with DMPS (by 50%).

In spite of the marked differences in the pattern of action of DMPS and DDC, both agents increase survival of rats after acute lethal doses of ^{210}Po by a factor of at least two[4,5], which is comparable to the effect of BAL[2]. This detoxifying effect might be due to the translocation of ^{210}Po from radiosensitive tissues, such as bone marrow and spleen, to the more resistant ones[2]. An additional radioprotective action sensu strictori of the compounds due to the sulfhydryl groupings could not be proved unequivocally in the case of ^{210}Po-intoxication[4]. Taking into account the late effects[11] of ^{210}Po, treatment with DMPS seems not advisable, since it induces renal lesions in rats and potentiates the toxic effect of ^{210}Po on the kidneys, resulting in nephrosclerosis[12]. The same might hold for MPG and PA. Since, however, the retention of ^{210}Po by the kidneys is reduced by DDC, a combined treatment might be advantageous. Corresponding experiments are now under way[9].

Zusammenfassung. Es wurde der Einfluss verschiedener intraperitoneal oder peroral verabreichter Chelatbildner auf die Verteilung von ^{210}Po im Organismus der Ratte untersucht. Die Wirksamkeit nimmt in der Reihenfolge: 2,3-Dimercaptopropan-1-sulfonat > Diäthyldithiocarbaminat > 2-Mercaptopropionyl-glycin > D-Penicillamin ab, während Diäthylentriaminpentaacetat sich als unwirksam erwies.

V. VOLF

Institut für Strahlenbiologie, Kernforschungszentrum, Postfach 3640, D-75 Karlsruhe 1 (Germany),
27. July 1972.

[9] V. VOLF, Strahlentherapie (1973), in press.
[10] A. CARLSSON, K. FUXE, T. HÖKFELT and M. LINDQVIST, J. Pharm. Pharmac. *18*, 60 (1966).
[11] V. A. SANOTSKII, E. V. ERLEKSOVA, Med. Radiol. *8*, Nr. 7, 71 (1963).
[12] Z. I. POLUBOYARINOVA, V. N. STRELTSOVA, Med. Radiol. *9*, Nr. 7, 22 (1964).
[13] D. B. DUNCAN, Ann. math. Statist. *32*, 1013 (1961).