government agencies, airports, and other facilities. Such samples may provide estimates of Sr^{90} deposition that are low by a factor of 2 to 10, compared with the deposition in adjacent areas.

The highest values for Sr^{90} in these samples consistently come from the tropical zone at the eastern base of the mountains. This suggests, since the moisture moves into that region from the east across the entire continent, that a greater portion of the fallout moves from east to west in this part of the southern hemisphere. This is consistent with general global circulation patterns for these latitudes. Perhaps the major portion of the fallout on the South American continent may be found in the interior tropical regions, although the path of circulation from the point of origin is obscure.

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References and Notes

1. Samples were collected under sponsorship of the Division of Biology and Medicine of the U.S. Atomic Energy Commission and the National Science Foundation. G. W. Prescott and R. W. Hodges aided in collection of samples. E. R. Ebersole, P. B. LeFleur, and W. C. Pierce carried out chemical analyses. The method of analysis was essentially the soil leach procedure described in *NYO-4700* (1957).
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Decarboxylase Inhibition and Blood Pressure Reduction by α-Methyl-3,4-Dihydroxy-DL-phenylalanine

Abstract. α-Methyl-3,4-dihydroxy-DL-phenylalanine has been found to be an effective inhibitor of aromatic amino acid decarboxylation in man. This was shown by decreased formation of serotonin, tryptamine, and tyramine from the precursor amino acids. Reduction of amine biosynthesis is associated with lowering of blood pressure in hypertensive patients and a transient sedative effect.

The aromatic amines impinge on almost every area of biological and medical interest. Two basic approaches to the study of amine metabolism, which have had interesting and practical implications in man, are depletion of tissue stores of amines by the rauwolfia alkaloids and inhibition of the degradation of amines by monoamine oxidase inhibitors. Since decarboxylation of an amino acid is a requisite reaction in the biosynthesis of aromatic amines, decarboxylase inhibition seemed to offer a third biochemical approach in this area and one which had not been explored previously in clinical studies.

Table 1. Inhibition of the decarboxylation of three amino acids by α-methyl-dopa. Values represent micrograms of amine excreted in the urine during an 8-hour period. For tyramine and tryptamine they represent the average of two experiments and for serotonin an individual experiment.

Patient	Urinary serotonin (after infusion of 30 mg of 5-hydroxy-DL-tryptophan)		Urinary tyramine (after L-tyrosine 125 mg/kg orally)		Urinary tryptamine (after L-tryptophan 50 mg/kg orally)	
	Control	α-methyl-dopa	Control	α-methyl-dopa	Control	α-methyl-dopa
V.K.			968	262	373	180
R.E.	3086	1347	1090	155	503	200
E.C.	2423	649	422	78	52	31
J.W.	2806	1086	750	124	56	30
H.F.	3570	1315				

A number of compounds are known to inhibit decarboxylation in experimental animals (*1, 2*). Of these α-methyl-3,4-dihydroxy-DL-phenylalanine (α-methyl-dopa) was selected for possible administration to humans. This compound, synthesized by Stein, Bronner, and Pfister (*3*), was first shown to be an effective inhibitor of dihydroxyphenylalanine decarboxylation in vitro by Sourkes in 1953 (*1*), an effect which was subsequently confirmed pharmacologically (*4*). Inhibition of 5-hydroxytryptophan decarboxylation was also demonstrated (*5*), and a decrease in brain serotonin levels was observed after parenteral administration of this inhibitor to mice (*6*).

Techniques for the measurement of amino acid decarboxylation in man have been developed recently in this laboratory. Preparatory to clinical investigations of α-methyl-dopa, chronic toxicity studies were performed by the Merck Sharp & Dohme Laboratories, and the compound was found to have a wide range of safety. α-Methyl-dopa was then administered to hypertensive patients at the Clinical Center. It was found to be a highly effective inhibitor of aromatic amino acid decarboxylation in man and to have hypotensive and sedative properties.

The decarboxylation of 5-hydroxytryptophan, tyrosine, and tryptophan was investigated by measuring the urinary excretion of their respective amines (serotonin, tyramine, and tryptamine) after administration of the precursor amino acid. L-Tryptophan and L-tyrosine were administered orally and 5-hydroxy-DL-tryptophan was given intravenously over a period of 90 minutes. Starting with administration of the amino acid, urines were collected for a period of 8 hours. During this time, the patients received a diet low and constant in tryptophan and tyrosine. When all control studies were completed, single 2.0-gm doses of α-methyl-dopa were administered daily. After at least 2 days of treatment with the inhibitor, the individual amino acids were administered again and urine was collected as before. In each case, the amino acid was given 2 hours after the last dose of α-methyl-dopa. Urinary serotonin was isolated from small aliquots of urine on an IRC-50 (NH_4+) column, eluted with 1*N* HCl, and assayed fluorimetrically (*7*). Tryptamine (*8*) and tyramine (*9*) were assayed by methods developed previously in this laboratory.

As shown in Table 1, amine formation after administration of all three amino acids was decreased by α-methyl-dopa, the decreases averaging 63 percent for 5-hydroxytryptophan, 80 percent for tyrosine, and 50 percent for tryptophan. α-Methyl-dopa also reduced the excretion of tyramine 50 to 85 percent in comparable 8-hour periods during which loading with tyrosine was omitted. The possibility existed that the effect of α-methyl-dopa on the excretion of amines might be due to

Table 2. Reduction of blood pressure by α-methyl-dopa.

Patient	Dose (gm/day)	Average blood pressures (mm-Hg)				Change	
		Control (placebo) week		Final week of drug		Lying	Standing
		Lying	Standing	Lying	Standing		
V.K.	2.0	159/93	168/102	135/79	122/82	−24/−14	−46/−20
F.J.	1.5 −2.0	173/94	169/104	136/82	116/81	−37/−12	−53/−23
F.N.	0.75–2.0	244/140	220/146	229/147	171/117	−15/+7	−49/−29
R.E.	1.0 −2.0	140/97	142/107	119/80	120/90	−21/−17	−22/−17
H.C.	1.5 −2.5	202/128	177/130	196/127	142/113	−6/−1	−35/−17
J.M.	2.0 −4.0	208/122	191/123	212/143	144/107	+4/+21	−47/−36
E.C.	2.0 −3.0	155/98	150/104	133/79	109/78	−22/−19	−41/−26
E.B.	2.0 −3.25	208/126	196/125	227/121	170/109	+19/−5	−26/−16
H.J.	2.0 −2.5	154/114	144/111	147/110	122/89	−7/−4	−22/−22
R.P.	3.0 −6.0	227/142	220/141	200/113	170/114	−27/−29	−50/−27

alterations in amino acid transport. However, measurement of tyrosine blood levels (*10*) in two patients following tyrosine administration showed that α-methyl-dopa did not affect the absorption of tyrosine from the intestine; in all cases the values rose to more than 5 times control levels. In other studies, it was shown that α-methyl-dopa did not influence the uptake of tyrosine by brain and muscle (*11*).

The effect of α-methyl-dopa was also reflected in a lowered excretion of 5-hydroxyindoleacetic acid and indoleacetic acid after the 5-hydroxytryptophan and tryptophan loads. The inhibitor did not influence the renal clearance of these acids. To ascertain further the effect of α-methyl-dopa on 5-hyroxytryptophan decarboxylation, the inhibitor was administered to two patients with metastatic carcinoid. A greater than fivefold increase in urinary 5-hydroxytryptophan and a decrease in urinary 5-hydroxyindoleacetic acid were observed in both cases (*12*).

Since the initial studies were carried out on hypertensive patients whose blood pressures were regularly measured, it became immediately apparent that α-methyl-dopa was a hypotensive agent. Accordingly, the blood pressure effects of α-methyl-dopa were investigated in ten hospitalized patients with primary hypertension. The lying and standing blood pressures were recorded four times daily. Placebo medication was given in pre- or posttreatment control periods, or both. α-Methyl-dopa was administered orally for periods of 7 to 28 days, initially as a single daily dose but later in divided doses at 8-hour intervals.

A summary of the blood pressure alterations produced by α-methyl-dopa is presented in Table 2. Appreciable reduction of the standing blood pressure occurred in all cases. In addition, a lowering of recumbent pressures was observed in five of the patients. In two patients (F. J. and F. N.), the postural hypotension was of such a magnitude as to necessitate reduction of dosage. For a period of 24 to 72 hours after initiating α-methyl-dopa, or after increasing its dosage, all patients had a temporary change in mental status, apparent to observers and manifested as sedation, tranquility, or fatigue. These obvious central effects seemed limited to the first 72 hours but further evaluation is required to determine whether more subtle effects may persist beyond that period.

These studies demonstrate unequivocally that aromatic amino acid decarboxylation can be inhibited in man by α-methyl-dopa, and indicate once more a relationship between amine metabolism and blood pressure regulation. The sedative effects of the drug are also in line with current thoughts concerning the role of amines in brain function. The effect of α-methyl-dopa on blood pressure has been of a sufficient magnitude to warrant extensive therapeutic evaluation of this compound and related aromatic amino acid decarboxylase inhibitors in hypertension. In fact, therapeutic trials in all disorders characterized by a relative or absolute excess of aromatic amines are indicated (*13*).

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11. We are greatly indebted to Dr. Gordon Guroff for carrying out these experiments.
12. A description of details of the latter studies is in preparation.
13. The technical assistance of Mrs. Consuelo Mullenberg is gratefully acknowledged. The Merck Sharp & Dohme Reseach Laboratories generously supplied the α-methyl-dopa (MK-350) for these studies.

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Behavior in the Cold after Acclimatization

Abstract. Experimentally naive albino rats begin to press a lever for short bursts of radiant heat earlier in a 16-hour session at 2°C than rats that have been living at this temperature for about a month. This difference reflects the different rates at which body temperature in the cold falls in acclimatized and nonacclimatized animals.

If a rat's fur is clipped, and the rat is then put into a cold environment (2°C), it will almost always die within 24 hours. If, however, it has lived in the cold for at least a month before being clipped, it will probably survive (*1*). Adaptation of this kind is called acclimatization. The present experiment examines the way this physiological acclimatization is accompanied by changes in thermoregulatory behavior (*2*).

Sixteen male albino rats from Sprague-Dawley stock, about 100 days old, were each given one 16-hour trial in a heat reinforcement chamber (*3*) located in a room maintained at 2° ± 1°C. While in this chamber, the rat, by pressing a plastic lever, could get 2-second bursts of radiant heat from a 250-watt infrared lamp (red bulb) located 10 inches above the floor of the chamber. Each press of the lever gave it one such burst; presses made while the lamp was on had no effect. The animals had received no previous experimental experience.

Eight of the 16 rats (randomly chosen) lived at 2°C for from 30 to 41 days before their experimental sessions. The other eight lived at 25°C. All were housed two or three to a cage and had free access to food (Purina Lab Chow) and water. Eight hours before an animal from the acclimatized group started an experimental session it was removed from the cold room to a cage near the control animals. This was done to make conditions immediately prior to the session comparable for the two groups (*4*). The rats were clipped completely with an electric clipper about 30 minutes before a session began.

During the first half-hour in the chamber the rats obtained between 4 and 25 reinforcements; the means for the control and acclimatized groups (13.0 and 16.8, respectively) did not differ significantly ($p > .30$). Almost all of these reinforcements occurred in the first few minutes. From then on most rats responded only occasionally until they made an abrupt transition to a steady rate. These data on early responding make it unlikely that differences in the time required to achieve a steady rate were due to differences in activity.

Acclimatized rats generally waited longer than control rats before starting to work at a steady rate for heat. The individual curves in Fig. 1 are ranked in terms of these latencies. The difference in latency is significant at the .01 level by a Wilcoxon unpaired replicates test (*5*).

All eight of the normal rats, but only five of the acclimatized rats, had been responding steadily for at least an hour by the end of the 16-hour session. The mean rates for these two groups were 5.6 reinforcements per minute (S.E. = .24) for the acclimatized rats, and 6.3 reinforcements per minute (S.E. = .52) for the control rats. This difference is not significant ($p > .20$).

Carlton and Marks reported that rats exposed to cold for 10 days turn on a heating device more frequently than rats living at room temperature (*6*). As they themselves have noted, this behavior was probably due to the fact that acclimatization was so incomplete at 10 days that rats were still losing weight at that time (*7*), and weight loss