veins, the heart rate started to increase. The rate gained rapidly to 250 and 270 beats/min. The high heart rate persisted in each instance in excess of 230 beats/min for several minutes. The fetus was then bilaterally adrenalectomized, with the results shown in Fig. 2.

After adrenalectomy, occlusion for 44 sec of the umbilical vessels, arteries first, veins next, resulted in a 20-sec delay in onset of recovery after venous occlusion with return to a rate only 9 beats/min in excess of the pre-occlusion rate (204 vs. 195). After arterial occlusion, there was a delay of 66 sec before a rapid recovery set in. The rate then rose to 220 beats/min. This was maintained for a period of about 10 sec. In both cases, the heart rate returned in 3 min to about 200 beats/min. The curve of heart rate decay with complete cord occlusion and no release is indicated by the circles in Fig. 2. The fetus struggled in each instance just prior to the onset of recovery of the heart rate.

This experiment shows that the latent period for onset of recovery of the denervated heart slowed by circulatory distress is prolonged and that the rate of the heart on recovery is less after adrenalectomy than it is before. The conclusion is clear that, in the case of the lamb fetus near term, a supporting physiological mechanism that helps to overcome the effects of acute circulatory distress is the release of a cardiac stimulating agent from the adrenal gland. This could be only epinephrine or a related substance.

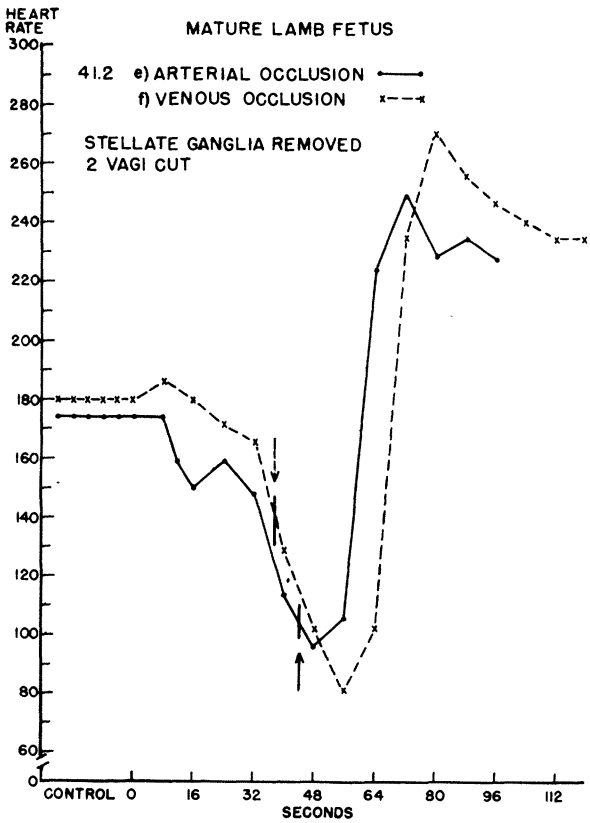

FIG. 1. Curves of heart rate recovery after temporary umbilical artery (——) and vein (x—x) occlusion. Release indicated at arrows. See text for description of prompt and extreme acceleration of heart rate. Mature fetal lamb at term, fetal condition, with 2 vagus nerves and stellate ganglia excised.

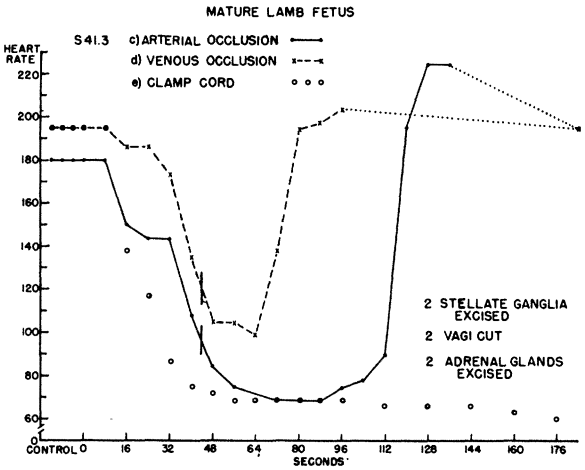

FIG. 2. Same as Fig. 1 except that both adrenal glands were likewise removed. Note long delay in recovery, especially after arterial occlusion, and small increase above pre-occlusion heart rate.

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Resolution of Isopropyl Nor-Adrenaline into Optical Isomers and Their Pharmacological Potency Ratio

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The resolution into optical isomers of sympathomimetic amines of the type

$$(OH)_2—C_6H_3—CHOH—CH_2—NH—R$$

has been performed for several terms of the series. Among these are epinephrine (*1*) and arterenol (*2*), but it is still an open problem for isopropyl noradrenaline. Since this drug differs markedly from the compounds involved in the sympathetic transmission of nerve impulse (*3, 4*), especially as far as its hemodynamic properties are concerned, it seemed worth while to resolve the racemate into its optical active components and to see if the L isomer would be more potent than the D form, akin to epinephrine and arterenol, or if another condition occurs.

By proper management of solvents and temperatures, the separation succeeded in the following manner: 22.1 g of the racemic base were treated with a solution of 15.5 g D-tartaric acid in 50 ml absolute

methanol. After the product had reacted, the liquid was cooled and left in the ice-box for several hours. A thick precipitate appeared. This was filtered, washed with methanol, and dried. The white-yellowish product obtained had $[\alpha]_D^{20} = +22°$; it was redissolved in methanol at 50–60° C and put into the ice-box again for several hours. The precipitate formed was then quite white and had $[\alpha]_D^{20} = +31.2°$. After a third recrystallization from diluted methanol, 10.2 g of white leaflets was obtained, with the following constants: $[\alpha]_D^{20} = +35.9°$; m.p. = 110–120° (with decomposition); *N* calc.: 3.87 (as bitartrate), found 3.78.

The free base D isopropyl nor-adrenaline, prepared from the bitartrate, gave: m.p. = 164–165° (with decomp.); *N* calc.: 6.66 found 7.07; $[\alpha]_D^{20} = +48.8°$ (as chlorohydrate).

The methanolic solutions containing the levoisomer were dried, the residue dissolved in H_2O, and the free base liberated with NH_4OH. After standing, the crystals were filtered and washed to obtain a white product that showed $[\alpha]_D^{20} = -42°$. They were dissolved in diluted HCl and precipitated again with NH_4OH; 3.6 g of white microcrystalline powder was obtained with the following constants: m.p. = 162–164° (with decomp.); *N* calc.: 6.66 found 7.07; $[\alpha]_D^{20} = -50°$ (as chlorohydrate).

For the pharmacological assays the D isomer as bitartrate, the L isomer as chlorohydrate, and the racemate as sulfate were employed. Equimolecular solutions were prepared and injected intravenously into tracheotomized dogs under light chloralose anesthesia. The vagi were cut and the arterial blood pressure was recorded with mercury manometers.

No tachyphylactic phenomena have been observed; a slight degree of racemization occurs for the solutions of L isomer: 7–12% after 3–5 months. For this reason only fresh solutions were used for the comparison of potency.

The percentage decrease in the blood pressure as a function of the amount administered in micrograms of free base per kilogram body weight has been taken into account for this comparison; furthermore, the duration of the effects observed, i.e., the time required for the blood pressure to revert to its initial value, has also been considered for a better evaluation of potency. This time, in seconds, multiplied by the percentage variation in the blood pressure, yields a quantity *A* (= amount of action) whose log is linearly related to the log dose, as clearly shown by the following regressions:

L isomer: $y = 3.35187 + 0.46124x$; $r = +0.954$; $P < 0.01$
Racemate: $y = 3.26252 + 0.38248x$; $r = +0.952$; $P \simeq 0.01$
D isomer: $y = 0.79125 + 1.16049x$; $r = +0.999$; $P = 0.001$

where $y = \log A$ and $x = \log$ dose.

Deviation from parallelism (shown by the numerical value of the regression coefficient) prevents any comparison of potency, unless the "amount of action," for which the comparison is made, has not been previously fixed. Taking for this amount arbitrary values we obtain:

Potency ratio	log *A*		
	3.0	3.5	4.0
Levo/racemate	1.336	2.095	3.28
Levo/dextro	317.5	87.45	24.6

Since racemates usually are pharmacologically half as potent as one of the optically active isomers (the latter being almost inactive or displaying different properties), the figures of the second row in the table seem to be more reliable.

The optical and pharmacological behaviors of isopropyl nor-adrenaline, as regards the differences between racemate and L isomer, also run quite parallel to those of epinephrine and nor-adrenaline, although the former are pressure-decreasing and the latter are pressure-increasing compounds. The D isomer, on the contrary, appears to be about 90 times less potent than the L isomer, whereas the values which have been put forward for the L/D potency ratio (as regards the blood pressure effects) are 12–15 (*5*) and 15–30 (*6*) for epinephrine; 25–33 (*7*) and 40 (*8*) for nor-adrenaline. These differences probably may be accounted for by differences in the racemization rates of these compounds in body fluids.

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Accumulation of Phenylalanine by a Phenylalanineless Mutant of *Escherichia coli*

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While studying aromatic biosynthesis with nutritionally deficient mutants of *Escherichia coli* (communior) isolated in our laboratories by the penicillin method of Davis (*1*), it was found that a mutant strain requiring phenylalanine for growth (M-Ph601) accumlates a considerable amount of that very substance, when cultivated in Davis' minimal medium (*2*) supplemented with a limited amount of the amino acid. It therefore resembles the similar mutant reported by Simmonds (*3*).

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