This method of detecting influenza virus may be of use where tissue-culture methods are deemed more suitable than isolation by means of the embryonated egg. However, we wish to point out that the egg isolation method has been found by us to be many times more sensitive. The stock virus A/NS/45/57, containing 80 HA units per milliliter and with an end-point titration by the adsorption-hemagglutination method of about $10^{-3.1}$, has an egg infective dose 5 percent of close to 10^{-8}.

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Instantaneous Linear Velocity of Flow in Pulmonary Artery Measured by a Catheter Tip Method

Abstract. Measurements of the instantaneous linear velocity of blood flow in the pulmonary artery of the human have not been reported previously. This report describes a catheter tip method for making such measurements.

A double-lumen catheter was designed (*1*) with one opening in the tip and the other 4 mm from the tip on the side of the catheter. When the catheter is positioned in the pulmonary artery, the pressure recorded from the tip is less than that from the side opening, because of the "drag" of the blood flowing past the tip. Accordingly, in this method, the catheter is used as a Pitot tube facing away from the approaching stream rather than into it as in the usual application of the Pitot tube. With the use of standard pressure transducers of equal sensitivity it is possible to record the difference in pressure which exists between the tip and side openings. The pressure difference is related to the velocity of the stream at the tip of the catheter by the equation

$$v = c(2g\Delta p)^{1/2}$$

where v is the velocity, g the gravitational constant, Δp the recorded pressure difference, and c a constant, all expressed in consistent units. The value of c, 0.3 for forward flow, was determined by repeated, reproducible measurements of Δp with the catheter in a long straight tube through which water was forced at different, known rates of flow. The catheter in this, and in other studies made with pulsatile flow, tended to seek the axis of the tube and showed a minimum of vibratory motion or "whip." Nor was significant whip noted in the measurements in the pulmonary artery reported here. For retrograde flow, a value of 0.8 was assumed for c.

In Fig 1 are shown the almost superimposed pressure tracings from the two lumina of the catheter, obtained in the pulmonary artery of an adult. The zero point of the pressure curve from the tip was arbitrarily displaced slightly above that of the pressure curve from the side opening so that the pressure tracing from the tip lies below that from the side opening only during periods of rapid forward flow, when the tip pressure was so reduced by the "drag" as to offset the displacement of the zero point. The pressures were recorded at two points, one close to the pulmonic valve, the other in a major branch of the right pulmonary artery, well distal to the valve. Shown below the pressure tracings in Fig. 1 are the corresponding curves of the difference in pressure between the tip and side openings.

The pressure tracings recorded from the two sites in the pulmonary artery are technically satisfactory. Aside from slight differences in the systolic and diastolic pressures, they differ chiefly in that the dicrotic notch and the succeeding rise in pressure occur later in the tracings from the distal position. The differential pressure curves differ in several respects. Close to the valve, there is a rapid increase in the velocity of ejection immediately following the onset of systole. The maximum velocity (29 cm/sec) occurs just prior to the pressure maximum; the velocity then decreases rapidly to zero. The entire period of forward flow lasts 0.2 sec and ends just before the appearance of the dicrotic notch. There follows a period of backward flow lasting just over 0.1 sec and ending with the completion of the dicrotic notch. It is succeeded by a short period of lesser forward flow, which, in turn, is followed by two or three small oscillations before the start of the next ejection. The duration and timing of the backward flow suggest that it is associated with the retrograde movement and closure of the semilunar cusps.

These curves differ from the only other published curves of instantaneous velocity in the pulmonary artery (*2*) in that back-flow is a significant feature of the curves presented here, whereas the curves of Baxter and Pearce, obtained in dogs with an implanted Pitot tube in the usual orientation, showed no back-flow.

In the pressure tracings from the distal point in the right pulmonary artery, the dicrotic notch and the postnotch rise in pressure are seen to occur later than in the tracings taken close to the valve. In fact, with some of the beats, the postnotch rise merges with the systolic rise of the next beat. That this rise is not due to atrial systole is shown by the lack of any constant temporal relationship between the rise in pressure and the appearance of the P-wave. Examination of the differential pressure curve shows that there is a significant forward flow associated with the post notch pressure rise, suggesting that this flow is due to a surge of blood rebounding from the valve and the arterial segment immediately distal to the valve following the retrograde flow noted above and the sudden closure of the valve. The systolic flow rises to a maximum (22 cm/sec) in two steps and returns quickly to minimal flow, the whole ejection lasting just over 0.3 sec. No sign of more than momentary and insignificant retrograde flow is noted at this point in the artery.

The method is not technically difficult. A properly modified double-lumen catheter is required in which the dynamic characteristics of the two lumina are identical. Pressure transducers of equal sensitivity connected to a recording apparatus that can produce a signal pro-

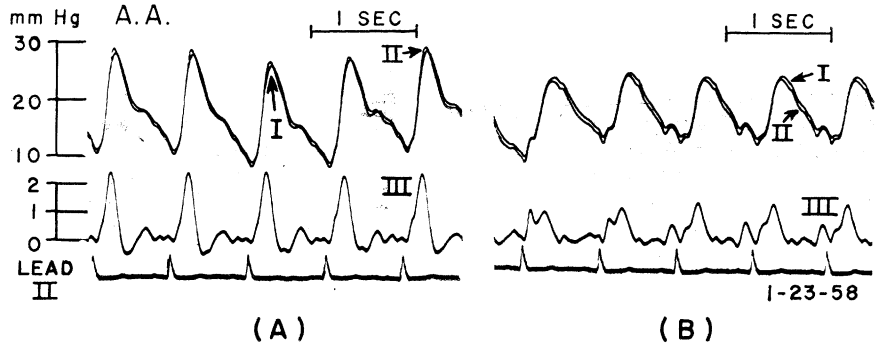

Fig. 1. (*A*) Catheter just distal to pulmonic valve. Curves I and II, pressures from tip and side openings, respectively. Curve III, differential pressure (note different scales). (*B*) Catheter in branch of right pulmonary artery. Curves same as in *A*.

portional to the difference between the signals from the transducers are also needed. The most troublesome problem has been the elimination of any factor tending to modify the dynamic characteristics of one lumen with respect to the other. Very fine bubbles in the system that do not visibly affect the pressure tracings can so change the characteristics of one lumen that the differential pressure tracing is seriously degraded.

It is believed that the method provides a means of measuring the instantaneous linear velocity in any vessel having a significant rate of flow. Volume flow per beat, such as the stroke volume in the pulmonary artery, can be calculated from the differential pressure curves if some estimate of the diameter of the pulmonary artery is available. A square-front velocity distribution is assumed in such calculations because of the pulsatile nature of the flow (*3*). Values obtained can be checked by standard Fick output studies.

The method appears to have applicability in normal and pathological situations, in steady and nonsteady states, in animals and in man.

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O-methylation, the Principal Route of Metabolism of Epinephrine in Man

Abstract. Evidence is presented which indicates that the principal pathway of metabolism of epinephrine in man is O-methylation to metanephrine. The extent of the conversion to metanephrine, a physiologically inactive compound, indicates that the enzyme responsible for this reaction, catechol-O-methyl transferase, is the enzyme mainly involved in the termination of action of epinephrine in man.

For many years monoamine oxidase has been considered to be the primary enzyme in the metabolism of epinephrine. However, recent work in this laboratory has demonstrated that epinephrine and norepinephrine are transformed in the rat mainly by O-methylation to yield metanephrine (*m*-O-methyl-epinephrine) and normetanephrine (*m*-O-methyl-norepinephrine) (*1*). This reaction has been shown to be catalyzed by the enzyme, catechol-O-methyl transferase (*1, 2*). It was of interest, therefore, to determine the extent of O-methylation of epinephrine in man.

Table 1. Fate of β-H^3-epinephrine in man.

Subject	Radioactivity excreted in urine				
	As percent of administered dose	Percent of urinary radioactivity present as:			
		Metanephrine			VMA†
		Free	Conjugated	Total*	
		β-H^3-epinephrine administered			
R.C.	95	13	46	59	30
D.K.	95	14	38	52	37
R.B.	88	11	36	47	35
D.H.	73	10	49	59	40
		β-H^3-metanephrine administered			
W.N.	92	16	39	55	24
K.S.	88	11	33	46	25

* Metanephrine found after heating in 1*N* HCl for 30 minutes at 100°C. Conjugated metanephrine represents the difference between free compound and total. A small amount of metanephrine glucosiduronic acid (6 percent) is included in the conjugated fraction.
† 3-Methoxy-4-hydroxymandelic acid (vanillylmandelic acid). This fraction also contains an unidentified metabolite which represents about 5 percent of the total radioactivity in the urine.

One milligram of *d,l*-β-H^3-epinephrine bitartrate (267 μc) was given intravenously over 45 minutes to four normal young male subjects, and the urine was collected for 48 hours. During this time, 73 to 95 percent of the administered radioactivity appeared in the urine (*3*). Metanephrine was extracted into isoamyl alcohol at *p*H 10, and the extract was assayed for radioactivity (*3*). On Whatman No. 1 paper the extracted radioactive material exhibited a single peak having the same R_F as authentic metanephrine (*1*) after chromatography in butanol–acetic acid–water (8:2:2) and isopropanol–5 percent ammonia (8:2). The 3-methoxy-4-hydroxymandelic acid was extracted at *p*H 1 into isoamyl alcohol. The extract was shaken with 5 percent sodium bicarbonate; the aqueous layer was re-extracted into isoamyl alcohol at *p*H 1, which was assayed for radioactivity (*3*). After chromatography, using the systems described above, the final extract showed a major peak having the same R_F as authentic 3-methoxy-4-hydroxymandelic acid and a small peak representing an unidentified compound present to the extent of 5 percent of the total radioactivity in the urine. All determinations of radioactivity were made by using internal standards and were corrected for the partitions of the O-methylated metabolites in the two-phase systems described above.

Free and conjugated metanephrine (Table 1) accounted for 54 percent of the radioactivity in the urine. These results differ from those published by others (*4*) in which little metanephrine was found in the urine following the infusion of C^{14}-epinephrine to man. We also found that 3-methoxy-4-hydroxymandelic acid accounted for 36 percent of the radioactivity in the urine (Table 1). Armstrong and McMillan (*5*) have reported the latter compound to be a major metabolite of norepinephrine.

To examine the relative importance of deamination in the metabolism of epinephrine, the metabolism of its major product, metanephrine, was studied.

About 0.7 mg of β-H^3-metanephrine (*6*) was administered intravenously to two normal young males over 45 minutes, and urine was collected for 48 hours. In contrast to the marked physiological and psychological effects produced by β-H^3-epinephrine, no detectable effects accompanied infusion of β-H^3-metanephrine. As in the case of β-H^3-epinephrine, 88 to 92 percent of the radioactivity was excreted in the urine. Essentially the same fraction of the administered radioactivity was excreted as metanephrine (free and conjugated) after administration of β-H^3-metanephrine as was found after administration of β-H^3-epinephrine (Table 1). A considerable proportion of administered metanephrine was deaminated and excreted as 3-methoxy-4-hydroxymandelic acid, indicating that a significant fraction of the metanephrine arising from epinephrine is further metabolized to 3-methoxy-4-hydroxymandelic acid.

These results indicate that the role of monoamine oxidase in epinephrine metabolism is mainly in the deamination of metanephrine. This would explain the observations that iproniazid, an inhibitor of monoamine oxidase, does not prolong the physiological actions of epinephrine in vivo (*7*).

From our results it can be concluded that the principal pathway of metabolism of epinephrine in man is its O-methylation to metanephrine, which in turn is conjugated and deaminated.