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S. SUMMARY OF DISCUSSION AND COMMENTARY

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An absence of relation between blood flow and the effect of adrenergic nerve stimulation was pointed out by Rosell. It is possible to prepare adipose tissue in the inguinal region of the dog with intact circulation and nerve supply. Under resting conditions the blood flow is comparable to that of skeletal muscle. Following sympathetic nerve stimulation at a physiological rate, a marked increase in release of FFA occurs together with vasoconstriction. The vascular effect is blocked by α- and β-blockers, the release of FFA by β-blockers. After injection of α-blockers, nerve stimulation produces a vasodilatation which may be inhibited by β-blockers (preliminary note in Nature **205:** 178, 1965).

Pekkarinen gave new evidence about the effect of hypoglycemia (induced by insulin in man) on excretion of catecholamines and metabolities; he and his associates confirmed that epinephrine (E) secretion is much more affected than that of norepinephrine (NE). Phenothiazines inhibit this reaction. Various detailed clinical observations (one case of essential increased NE secretion; surgical shock, cardiac insufficiency, pregnancy, heavy muscular exercise) show that there is no parallel between activation of the adrenal cortex and the secretion of catecholamines.

Brodie has brought new information about the sensitization to catecholamines by thyroid hormones. The reporter points out that one must consider carefully the system with which one is working. A first system is the whole mammal tested by intravenous injections of catecholamines. The fate of the population of injected molecules may be very different: a) uptake and storage by the granules in nerve endings, b) reaction with specific receptors and subsequent inactivation by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), or c) inactivation by the same enzymes without previous reaction with receptors.

A large fraction of the injected molecules may be lost by being metabolized after crossing cell membranes at a place devoid of receptors. Nobody speaks of this possibility; nobody knows how important this fraction may be. A shift from that population of physiologically unimportant molecules to that of group *a* or *b* may affect considerably the physiological effect of a given dose of catecholamine. The sensitizing action of metanephrine and normetanephrine to α-effects of catecholamines may be interpreted along these lines (Z. M. Bacq and J. Renson, Arch. internat. Pharmacodyn., **130:** 385, 1960).

A second system is the isolated organ, perfused or not, intact or not, in which one controls strictly the composition of the external medium. In this case, generally, the quantity of catecholamines introduced in the system is large enough to compensate for the molecules lost or taken up by granules and the concentration offered to the receptors is stable.

There is a third system, developed by G. L. Brown and his associates (J. Physiol. **138:** 81, 1957) in which the circulation of the spleen is controlled in

the intact cat; one can collect all the blood that passes in the organ before, during, or after a period of physiological stimulation of the adrenergic nerves. What one measures in this system is the number of molecules of NE released by nerve stimulation which have *escaped* the various mechanisms of uptake and metabolism. The uptake by granules in nerve endings is probably small because the nerves are constantly stimulated. Thus this system is particularly well suited to study the variations of the fraction which reacts with the receptors. It is a classical fact that injection of an α-blocker increases enormously the "escape" of NE, and this coincides with inhibition of the effect of nerve stimulation, that is to say, inhibition of the reaction with the receptor.

A less known fact observed with this technique is that COMT inhibitors (pyrogallol or catechol) do not change in the slightest way the amount of NE escaping during nerve stimulation (Z. M. Bacq, G. L. Brown, and C. B. Ferry, Compt. rend. Acad. Sc. Paris **250:** 194, 1960). One has here a situation in which the physiological response is greatly increased (Bacq, 1936) although the proportion of molecules reacting with the receptors remains the same. This fact also shows that when a molecule of NE has entered the receptor it cannot get back into the fluid around the cell.

In the reporter's opinion, the theory which explains the sensitizing effect of thyroid hormones to catecholamines by a decreased uptake followed by a longer contact of the amines with the receptors, must find its final "physiological" confirmation with a technique similar to that of Brown and associates.