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Report on the Discussion of the First Session

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A NEW procedure for assaying catecholamines that has great sensitivity and specificity has been presented by Costa. The amines are acylated and then separated by gas chromatography, and quantitation is by mass spectrometry. This procedure is by far the most sensitive available. For example, as little as 10^{-14} moles of norepinephrine (NE) can be accurately measured in a tissue sample. Costa also presented evidence that the calculation of the turnover rate of NE in the ventricle of the rat heart, based on the specific activity of tyrosine and NE in the heart after an intravenous injection of radioactive tyrosine, may be incorrect. His conclusion was based on the observation that calculations with other procedures, such as the decline of ^{3}H-NE from heart after an intravenous injection or the decline of endogenous NE after treatment with α-methyltyrosine, did not agree with the rate calculated by using the specific activity of tyrosine in the heart. In contrast, when the specific activity of dopamine (DM) and NE in the heart were used to estimate turnover, a rate was found that was compatible with the other procedures. By extrapolation, Costa predicted that the specific activity of the tyrosine from which the amines are formed must be greater than the specific activity of tyrosine in the whole heart. Costa's studies provide experimental support for the validity of estimating the turnover rate of NE in heart by using either α-methyltyrosine or ^{3}H-NE.

Spector showed the importance of the catecholamines in the blood vessels and contrasted the properties of this amine store with that of the heart. Apparently, the blood vessels cannot take up circulating NE as efficiently as the heart. Moreover, drugs that block the uptake of NE by heart are not as effective in blocking the uptake of NE by vessels. The catecholamines in vessels, therefore, must be synthesized in the vessels. In support of this hypothesis, Spector found tyrosine hydroxylase activity as well as monoamine oxidase and catechol-O-methyl transferase activity in the vessels. He also demonstrated that the NE in the vessels is formed at a rapid rate. The rapid rate of NE formation by the vessels probably explains the vast quantity of catecholamine metabolites found in the urine. Spector also suggested that tyrosine hydroxylase activity of vessels may be inversely related to blood pressure, whereas monoamine oxidase activity of vessels may be directly related to blood pressure. The sympathetic nerves of the vessels have not been as extensively studied as the nerves in other tissues, and Spector's observations are helping to shed light in this area.

Weiner presented compelling experimental support for product inhibition

of catecholamine synthesis *in vivo*. His studies suggest that free NE within sympathetic nerves inhibits tyrosine hydroxylase activity by competitive antagonism with an endogenous pteridine cofactor. Therefore, drugs that increase the concentration of free NE should inhibit catecholamine synthesis and adding a pteridine cofactor to the preparation should reverse the effects of NE on synthesis. This hypothesis was tested and found to hold true. Weiner also showed that tyrosine hydroxylase activity is enhanced during nerve stimulation and immediately after stimulation. The activation of tyrosine hydroxylase during nerve stimulation was partially blocked by adding exogenous NE to the preparation, thus supporting the concept of product inhibition as one of the physiological mechanisms that regulate catecholamine synthesis when nerves are activated. The poststimulation increase of NE synthesis was not blocked by adding exogenous NE to the preparation. Evidently product inhibition is not an important regulatory mechanism during this period.