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G. SUMMARY OF DISCUSSION AND COMMENTARY

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At the First Catecholamine Symposium in 1958, evidence was presented that the formation of noradrenaline (NE) or adrenaline (E) from tyrosine proceeded by a direct pathway—tyrosine → dopa → dopamine → NE → E. The obligatory nature of the above sequence of reactions was not established, however, until the substrate specificities of all the enzymes were elucidated, as reported in this symposium and in earlier communications. Although each of the enzymes, except tyrosine hydroxylase, has a broad substrate specificity, the overall requirements are such that alternative routes are ruled out, except to a possible minor extent in certain tissues (Axelrod, Section I J). For example, dopamine-β-hydroxylase can oxidize dopamine and *p*-hydroxytyramine respectively to NE and octopamine, but octopamine cannot be oxidized to NE by tyrosine hydroxylase, and when radioactive *p*-hydroxytyramine is given to rats radioactive octopamine but not radioactive NE is formed in sympathetic nerves.

Since various tissues contain an L-dopa-α-ketoglutarate transaminase and *meta*-hydroxylation of *p*-hydroxyphenylcarboxylic acids has been observed *in vivo*, Gey suggested the possibility of an alternate pathway for the formation of dopa; tyrosine → *p*-hydroxyphenylpyruvate (PHPP) → dihydroxyphenylpyruvate (DHPP) → dopa. In support of this he cited the observation made in his laboratory that when tyrosine-C^{14}, PHPP-C^{14}, DHPP-C^{14}, and dopa-C^{14} were administered to rats subcutaneously, the amounts of catecholamine-C^{14} and their 3-O-methyl derivatives found in brain, expressed as percent of C^{14} injected per gram of body weight, were, respectively, 0.4, 1.1, 1.6 and 1.2. Since many factors, such as isotope dilution, transport across the blood-brain barrier and transamination of PHPP to tyrosine, were not considered, the interpretation of these data is obscure.

Evidence that the rate of NE formation is controlled by the rate of NE secretion has been obtained in several laboratories. Welch reported that the catecholamine content of adrenal glands of cold-adapted rodents was higher than that of controls at ambient temperature even though the rate of catecholamine secretion was greater in the cold-adapted animal. More directly, Weiner found that, in the isolated vas deferens preparation, stimulation of the hypogastric nerve led to increased formation of NE and dopamine from tyrosine-H^3. The increase was found almost entirely in the tissue itself but a small increase was also found in the organ bath. Further, Musacchio found that NE formation from tyrosine, but not from dopa or dopamine, was decreased in decentralized rat salivary glands. These data provide evidence that the rate of NE secretion controls the rate of NE synthesis and that this control takes place at the level of the conversion of tyrosine to dopa.

The physiological role of ascorbic acid in the formation of NE is questionable

at the moment. Although Kaufman has very elegantly shown that ascorbic acid efficiently and stoichiometrically reduces the Cu^{2+} of dopamine-β-hydroxylase *in vitro*, several laboratories have reported that the formation of NE in scorbutic guinea pigs is not decreased. It may well be that ascorbic acid is only one of several compounds that can reduce dopamine-β-oxidase *in vivo*. Booker reported that a continuous infusion of dopamine into scorbutic guinea pigs failed to cause an increase in blood pressure and in ventricular contractile force, and that at the end of the infusion period the hearts of normal animals showed a 30 % to 40 % increase in NE, while the hearts of ascorbic acid deficient animals showed no change; these findings are consistent with a physiological role for ascorbic acid in promoting the rapid synthesis of NE. The further observations of Booker that ascorbic acid deficient guinea pigs required a longer time than normal animals to replenish the NE content of tyramine-depleted hearts is also consistent with ascorbic acid having a physiological role, but not an essential one, in the synthesis of NE. However, the indirect measurement of dopamine-β-hydroxylase activity in scorbutic animals does not necessarily indicate a requirement for ascorbic acid since other factors may be involved.

The oxidation of the tetrahydropteridines to a quininoid-like structure in their function as cofactors for tyrosine and phenylalanine hydroxylations offered Ellenbogen an explanation of his observations on the structural requirements of pteridines as cofactors for tyrosine hydroxylase. The addition of any substituent which prevents the formation of the quininoid structure will cause loss of cofactor activity. Thus, addition of an acetyl or formyl group at the 5 position, or methylation of the hydroxyl group at the 4 position resulted in loss of cofactor activity in several pteridines.