Relationships Between Alterations in Amine Metabolism and Blood Pressure

By Albert Sjoerdsma, M.D., Ph.D.

There has long been an appealing notion that naturally occurring pressor amines may be involved in some way in the pathogenesis of primary hypertension. While conclusions on this thesis have been drawn pro and con in the past, the fact of the matter is that we are only now beginning to emerge from an era of crude technique and inadequate information that largely precluded the attainment of meaningful results. The recent development of sensitive and specific methods of assay for some aromatic amines, the isolation and identification of “new” amines, and a more coherent understanding of the complex biochemical processes controlling the synthesis and degradation of amines are all factors that have led to new avenues of approach and broadening of concepts.

Since the hypertension of man may be unique, we have chosen to investigate the overall status of aromatic amine metabolism in the intact hypertensive human, attempting whenever possible to confirm and extend findings in experimental animals. Major focal points of the studies have been: (a) development of methods to assess overall synthesis and metabolism of aromatic monoamines, (b) differentiation by chemical means of cases of essential hypertension from that resulting from pheochromocytoma, and (c) determination of biochemical and pharmacological response in hypertensive subjects to the administration of certain enzyme inhibitors. This report presents highlights of these investigations.

Résumé of Aromatic Amine Metabolism

A schematic diagram (fig. 1) of amine metabolism will serve to illustrate certain principles. Included in this schema are such well-known compounds as serotonin and noradrenaline as well as more recently discovered amines, tryptamine, tyramine, and phenylethylamine. In each case, decarboxylation of a dietary amino acid is a requisite reaction for synthesis of the amine. Parenthetically, it should be noted that in some instances an intermediate compound is involved, e.g., 5-hydroxytryptophan in the case of serotonin and dopamine in the case of noradrenaline. Once formed, the amine may either be inactivated by storage in tissue depots or undergo metabolic degradation, locally or after diffusion, elsewhere. Oxidative deamination by monoamine oxidase (MAO) leading eventually to acid urinary metabolites is important in the metabolism of all aromatic monoamines known in man. Alternate pathways of metabolism also exist, the chief of these being O-methylation by catechol-O-methyl transferase in the case of the catecholamines.

From this brief summary, it can be seen that amine metabolism is subject to evaluation and attack at several points. In general, the overall endogenous production of an amine is measured best by the amount of the corresponding acid metabolite (e.g., 5-hydroxyindoleacetic acid from serotonin), which is excreted in the urine. The urinary excretion of the amine itself may also be an index of this, though usually it represents only a small percentage of the total production. For the catecholamines (norepinephrine and epinephrine), measurements in urine of 3-methoxy-4-hydroxyxymandelic acid (MOMA), the 3-methoxy-4-aminines (normetanephrine and metanephrine), and the catecholamines themselves provide a rather complete picture of daily synthesis and release. The discovery of inhibitors of the two enzymatic processes shown in figure 1, aromatic L-amin acid decarboxyla-
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tion and oxidative deamination, created a need for means of studying the condition of these reactions in man. One useful technique consists of administering the substrate and measuring the urinary excretion of the resulting product (i.e., amino acid → amine, amine → acid). This method has also been applied to evaluation of catechol-O-methylation, though an effective inhibitor of this reaction in patients has not become available. The urinary excretion of amines that are completely dependent on monoamine oxidase for their metabolism (e.g., tryptamine and tyramine) affords a sensitive index of the status of this enzyme in the body. Their excretion rises if monoamine oxidase is deficient or inhibited by a drug. Correlations between demonstrable enzyme inhibition and blood-pressure alterations in man will be dealt with in appropriate sections. Factors affecting inactivation of amines by storage in tissues, e.g., depletion by Rauwolfia alkaloids, will not be considered here.

Catecholamine Metabolism in Primary Hypertension

The role of the sympathetic nervous system in the mediation of neurogenic vasoconstriction and the therapeutic importance of drugs that interfere with sympathetic function have focused a great deal of attention on the neurotransmitter substance, norepinephrine. The question of whether an abnormality of norepinephrine production or inactivation exists in essential hypertension has frequently been raised but can now largely be answered in the negative. Some of the early confusion in this area was due to the fact that knowledge of the origin of urinary catecholamines was incomplete and methods of chemical assay were unreliable. The most extensive investigation in this field was reported in 1954 by von Euler, Hellner, and Purkhold. Employing bioassay techniques, they found that, while the excretion figures in 500 unselected patients with hypertension were mostly within normal limits, in about 15 per cent of cases the excretion of norepinephrine was higher than that found in normotensive subjects. A criticism of the study is that only total catecholamines (free plus conjugated) were measured. It has become known subsequently that ingestion of certain foods containing norepinephrine and other catecholamines may alter the excretion of conjugated, but not of free, catecholamines. A study of free urinary catecholamines in 21 selected hypertensives was reported from the same laboratory in 1957. No differences in the excretion of norepinephrine during night hours were found between hypertensive patients and normotensive subjects, and the values during the daytime were actually lower in the former group. In addition to showing the absence of a significant difference in urinary catecholamines between normotensive and hypertensive individuals, Gitlow et al. also found similar excretions of MOMA.

In the course of studies on pheochromocytoma, we had occasion to measure urinary catecholamines, total 3-methoxy-amines (normetanephrine plus metanephrine), and MOMA in many cases of essential hypertension. In a series of 114 hypertensive patients who were not acutely ill, the excretion of unconjugated catecholamines (norepinephrine plus epinephrine) was found to be $32 \pm 18$...
Table 1
Catechol-O-Methylation as Indicated by Excretion of 3-Methoxy-Isoproterenol (M.I.) after Infusion of d-Isoproterenol (I.).

<table>
<thead>
<tr>
<th>Case</th>
<th>Reclining B.P. (mm. Hg.)</th>
<th>Dose of I. (mg.)</th>
<th>Urinary M.I. as % of I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126</td>
<td>19.2</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>19.0</td>
<td>48</td>
</tr>
<tr>
<td>2*</td>
<td>196</td>
<td>20.4</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>19.6</td>
<td>49</td>
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<tr>
<td>3*</td>
<td>180</td>
<td>21.7</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>20.0</td>
<td>58</td>
</tr>
</tbody>
</table>

*During treatment with a monoamine oxidase inhibitor (β-phenylisopropylhydrazine, 25 mg./day).

μg./day (mean ± S.D.), which is clearly within the normal range. Only two patients were encountered with values greater than 100 μg./day, these being 115 and 117 μg./day respectively. In a second series of 121 patients (91 hypertensives and 30 normotensives), the excretion of total metanephrines was 0.62 ± 0.28 mg./day (mean ± S.D.). No statistically significant difference was found between the hypertensive and nonhypertensive groups, but the semiquantitative nature of the assay in this range makes the observation of questionable significance. In 20 hypertensives the excretion of MOMA was 3.7 ± 1.1 mg./day (mean ± S.D.), one patient had a value of more than 6.0 mg./day, this being 7.1 mg./day. Recently I have compared the urinary excretion of total metanephrines (free plus acid hydrolyzable) and MOMA in 13 cases of uncomplicated hypertension and 13 normal young adults. No significant differences between the two groups could be shown. In all cases the metanephrine values were less than 1 mg./day with an average of 0.60 mg./day (range, 0.36 to 0.79) in the hypertensives and 0.51 mg./day (range, 0.24 to 0.75) in the controls. Corresponding values for MOMA were 4.4 mg./day (range, 3.1 to 6.3) and 4.7 mg./day (range, 3.8 to 6.8) respectively.

It may be argued on clinical grounds that some patients, usually labile hypertensives, exhibit evidence of sympathetic overactivity during periods of elevated blood pressure and should therefore have an elevated excretion of urinary catecholamines and metabolites at this time. This phase of the problem has not been subjected to careful evaluation. However, such reactions often appear to be related to situations of stress that may result per se in elevated urinary catecholamines, in the latter condition, renal clearance of the acid is diminished.

Even in the absence of excess production of norepinephrine by the sympathetic nervous system, exaggerated vasoconstriction might occur on the basis of impaired enzymatic inactivation of the amine in arterioles. The possibility of a deficiency of catechol-O-methyltransferase as a cause for hypertension has been raised by Mendlowitz et al. The primacy of 3-O-methylation in the metabolism of circulating epinephrine has been conclusively shown by Axelrod et al., La Brosse et al., and Kopin. However, for circulating norepinephrine in man, Goodall et al. interpret their data as suggesting a more equal distribution of initial metabolism between O-methylation and oxidative deamination. For norepinephrine formed in tissues, some evidence favors monoamine oxidase rather than catechol-O-methyltransferase as being responsible primarily for local enzymatic inactivation. The fact that the excretion of the metanephrines represents a much smaller fraction of the metabolites in normal and hypertensive subjects than does MOMA seems to support the idea that monoamine oxidase is the primary means of metabolic degradation of norepinephrine formed at nerve endings.

Is there any evidence of a deficiency of monoamine oxidase or catechol-O-methyltransferase in hypertension? The finding of similar urinary excretory patterns of catecholamines and methoxy-metabolites in normotensives and hypertensives in itself speaks against this possibility. We have obtained additional information which suggests that, from the standpoint of overall amine metabolism, there is no deficiency of either enzyme.
in primary hypertension. When monoamine oxidase is effectively blocked with a drug in hypertensive subjects, no alteration in the urinary excretion of norepinephrine, epinephrine, or dopamine is observed, indicating that the alternate pathway of O-methylation is intact. In the same experiments, the levels of urinary tyramine and tryptamine increased greatly owing to complete dependence of these amines on monoamine oxidase for their metabolism. However, the urinary excretion of tryptamine and tyramine is not increased over normal in hypertension, suggesting that there is no overall deficiency of MAO in this disorder. In confirmation of this, we have found that the conversion of orally administered serotonin to urinary 5-hydroxyindoleacetic acid is not significantly different in the hypertensive and normotensive except in the presence of impaired renal function.

In the course of such studies, the need for a sensitive test of catechol-O-methylation in man became apparent. It was felt that a rather simple procedure might be devised using a catecholamine that would be metabolized exclusively by O-methylation and that could be given in rather large quantities intravenously without untoward reactions. The d-isomer of isoproterenol (Isuprel) was found suitable for this purpose. It was ascertained that 20 mg of this compound could be infused in patients over a period of 30 minutes with only moderate effect on blood pressure and pulse rate. The extent of O-methylation could be determined by measuring the urinary excretion of 3-methoxy-isoproterenol in the succeeding 12 hours. The results obtained in one normotensive and three hypertensive patients are shown in table 1. Although the data are preliminary, there is no indication of an overall deficiency of O-methylating activity in the hypertensive subject as measured by this method.

The following may be said in the way of conclusions and commentary. It seems certain that there is no excess production of norepinephrine in the usual case of essential hypertension. Likewise, while no direct studies of the enzyme activity of nerves and blood vessels in hypertension have been made, the absence of any overall defect in amine metabolism in terms of catechol-O-methylation and oxidative deamination argues against the existence of any local disturbance. Factors such as the degree of diffusion from sites of production and the inactivation by physiochemical processes require investigation.

We will now turn to the induction, in patients, of alterations in amine degradation and synthesis by chemical agents. In spite of the fact that the untreated hypertensive cannot be distinguished from the normal subject in biochemical terms, interference with amine synthesis and metabolism has been associated with lowering of blood pressure in hypertensive individuals.

Inhibition of Aromatic Monoamine Oxidative Deamination

A large number of new drugs categorically referred to as monoamine oxidase (MAO) inhibitors have been introduced into clinical medicine in the past four years. Individual compounds of this class are being promoted as psychic energizers, for use in treatment of angina pectoris, and as antihypertensives. Studies in this laboratory have been concerned at length with the relationship between inhibition of monoamine oxidase and changes in blood pressure. Emphasis has been given to the determination of whether or not a given dosage schedule of a new or established "MAO inhibitor" actually produces significant enzyme inhibition in patients. Lacking this information, meaningful interpretation of pharmacological response seemed impossible. A review of the techniques that have been applied to determining MAO inhibiting activity in man is presented elsewhere. The most convenient procedures have consisted of measuring the urinary excretions of certain amines, such as tryptamine and tyramine, that appear in the urine in increased amounts when their metabolism is blocked with an effective dosage of an MAO inhibitor.

In studies with eight different "MAO inhibitors" we have observed an orthostatic hypotensive effect rather uniformly when evidence
of effective MAO inhibition was demonstrable. Thus, when a compound is reported to have psychic-energizing or antiangina activity in the absence of hypotensive effects, we have come to doubt that effective MAO inhibition is being achieved in the dosage used or that the alleged effects bear any relationship to enzyme inhibition. There have been two recent instances in which this opinion proved to be correct.

Like the prototype MAO inhibitor, iproniazid, most of the compounds that have become available for clinical study are derivatives of hydrazine—H₂N-NH₂—and frequently produce toxic effects in man at the doses required to lower blood pressure. Because of this, the recent introduction of certain nonhydrazine MAO inhibitors may be a promising development. One such, N-benzyl-N-methyl-2-propynyl-amine-HCl (MO-911, A19-120) was discovered by Taylor et al.¹⁷ In preliminary experiments with Horwitz,¹⁸ Mo-911 proved an effective antihypertensive agent as well as a potent MAO inhibitor in man. Since the structure of this compound (fig. 2) is radically different from that of previous MAO inhibitors, the findings provide rather conclusive evidence of a causal relationship between MAO inhibition and lowering of blood pressure.

Since MAO inhibition results in the accumulation of various pressor amines in tissues, the blood-pressure lowering actions of MAO inhibitors seem paradoxical and require explanation. Clinically, blood-pressure alterations are predominantly orthostatic, pointing to decreased activity of the sympathetic nervous system. In animal experiments, which unfortunately bear little resemblance to the clinical situation, Gertner¹⁹ and also Goldberg and DaCosta²⁰ have demonstrated a selective inhibition of sympathetic ganglia with several MAO inhibitors. Possibly accumulation of an amine, e.g., serotonin or norepinephrine, in sympathetic ganglia is responsible for the effects observed in man. Other explanations can be offered but without documenting evidence. One which I favor is that dopamine, the precursor of norepinephrine, a weaker pressor substance and an excellent substrate for MAO, might accumulate at nerve endings and competitively block the action of norepinephrine released while standing.

Aside from the therapeutic implications, a major use of MAO inhibitors in man has been as biochemical tools in disclosing the presence of hitherto unidentified amines. The administration of effective doses of MAO inhibitors produces an increase in the urinary excretion of many amines for which effective alternate routes of metabolism are not available.¹⁴, ²¹ Several that have been identified in human urine utilizing this approach are listed in table 2. Relative to catecholamine metabolism, the natural occurrence of norepinephrine and synephrine is of greatest interest. These compounds differ in structure from norepinephrine and epinephrine only in lacking a meta-hydroxy group. A possible parallel in biosynthetic pathways has been suggested²³ and the physiological implications of the close chemical relationship of the synephrines to the catecholamines merit consideration.

From studies with MAO inhibitors the impression has been gained that decarboxylation to an amine is a pathway of metabolism for all dietary amino acids. Whether most of these amines have unique physiological functions or merely represent biochemical "appendices" is the challenge of the future in this field. Certainly, it is hazardous to consider the
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therapeutic effects of MAO inhibitors in relation-
tship to one or two of them.

Inhibition of l-Aromatic Amino Acid
Decarboxylation

Another chapter in the induction of alter-
ations of amine metabolism has been written
in this laboratory during the past year with the
successful inhibition of amine biosynthesis in
man by the administration of α-methyl-3,4-di-
hydroxy-dl-phenylalanine (α-methyldopa [α-
methyldopa]; structure shown in fig. 3).
The background of information that led to
this development, as well as the initial find-
ings, has been reported.24 Actually, α-
methyldopa has been available for animal ex-
perimentation since 1954 when, after its syn-
thesis by Stein, Bronner, and Pfister of the
Merek Institute, Sourkes showed it to be a
competitive inhibitor of the decarboxylation
doP
oi

\[ \text{Structure of α-methyldopa.} \]

The formation of dopamine from DOPA and serotonin was identi-
fied.27 No consideration had been given to clinical use of α-methyldopa, however, presumably because of the lack of interesting pharmacological ef-
fects of the compound in routine animal
screening programs.

We were interested in carrying out clinical
trials of this agent for two reasons: (a) to
explore the possibility that serotonin synthesis
might be inhibited in patients with malignant
carcinoid, and (b) to determine whether de-
carboxylase inhibition could be produced in
patients with this agent. In studies on urinary
amines during MAO inhibition, methods had
been developed that were applicable to the
determination of whether a compound might
interfere with the formation of amines from
their corresponding amino acids in man. Di-


\[ \text{H} \quad \text{CH}_3 \]

\[ \text{HO} - \text{C-COOH} \]

\[ \text{H} \quad \text{NH}_2 \]

\[ \alpha\text{-METHYL-DOPA} \]

again two hours after administration of single
2.0 Gm. doses of α-methyldopa orally, and
then to determine the amount of the corre-
responding amine excreted in the urine in the
following eight hours. As shown, the for-
mation of dopamine from DOPA and serotonin
from 5-hydroxytryptophan was consistently
diminished after treatment with α-methyldopa.

In addition to the chemical alterations men-
tioned, the sedative and hypotensive proper-
ties of the compound were observed for the
first time. In patients under continuous treat-
ment the central effects have occurred consist-
tently during the first 48 to 72 hours but di-


\[ \text{HO} - \text{C-COOH} \]

\[ \text{H} \quad \text{NH}_2 \]

\[ \alpha\text{-METHYL-DOPA} \]

\[ \text{H} \quad \text{CH}_3 \]

\[ \text{HO} - \text{C-COOH} \]

\[ \text{H} \quad \text{NH}_2 \]

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\[ \text{H} \quad \text{CH}_3 \]

\[ \text{HO} - \text{C-COOH} \]

\[ \text{H} \quad \text{NH}_2 \]
A more important question is whether a new biochemical basis for the development of antihypertensive drugs exists in the area of decarboxylase inhibition. Superficially, it seemed logical to suppose that inhibition of the synthesis of dopamine from DOPA was occurring in the patients, resulting in depletion of norepinephrine in the central and peripheral sympathetic nervous system, thereby producing a lowering of blood pressure. One group of experiments tends to confirm this supposition; they were based on the fact that the compound was initially supplied in the racemic form. After resolution of the compound into its d and l isomers (Merck, Sharp and Dohme Laboratories), chemical evaluations in patients showed the d compound to be inactive. The l isomer accounted not only for all the decarboxylase blocking effects but also for the hypotensive (and probably sedative) effects. Typical blood-pressure actions of the racemic, dextro, and levo forms of α-methyl-dopa are shown in fig. 5. A fortunate result is that the required dose of the compound can be reduced at least 50 per cent by employing the l isomer (Aldomet).

While a correlation between decarboxylase inhibition and hypotensive action is suggested by the aforementioned results, consideration of other factors indicated the problem to be more complex. In early clinical trials, it was noted that though a single oral dose (e.g., 1.0 Gm.) might fail to alter blood pressure, repetition of the same dose 24 and 48 hours later would often lead to a hypotensive effect. It seemed unlikely that decarboxylase inhibition could persist for 24 hours after a single dose, since blood levels of the compound were already low 8 hours after drug administration and negligible after 12 hours. Furthermore, presuming the turnover of norepinephrine in sympathetic nerves to be relatively rapid, it seemed inconceivable that norepinephrine depletion owing to block of synthesis would per-
Example of blood pressure responses to the racemic (dl), dextro, and levo forms of \( \alpha \)-methyldopa.

In unanesthetized dogs, Goldberg, DaCosta, and Ozaki\textsuperscript{30} of this laboratory showed that hypotension after intravenous injection of 100 to 200 mg./Kg. \( \alpha \)-methyldopa did not begin until two to three hours had elapsed and the maximum effect was not observed until four to six hours. Decarboxylase inhibition, as measured by blockade of the inotropic effects of l-DOPA, appeared immediately and was usually dissipated by the time hypotension developed. A one- to two-hour period of delay between the intravenous administration of \( \alpha \)-methyldopa and the development of hypotension has also been observed recently in human hypertensives. In the latter circumstance the blood-pressure effect has been apparent for as long as 24 hours. An action "above and beyond" decarboxylase inhibition is implied by these findings.

Unpublished observations by S. Udenfriend and associates in guinea pigs and rats show that, in addition to a blockade of synthesis,
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2-methyldopa and a related compound (2-methyl-m-tyrosine) may act on norepinephrine storage mechanisms. The decline and recovery of tissue levels of serotonin and dopamine after single doses of these inhibitors were found to occur over a period of hours and to parallel changes in decarboxylase activity. However, depletion of cardiac and brain norepinephrine persisted for three to four days and was maximal even after decarboxylase activity had returned to normal and the inhibitor had disappeared from the tissues. Thus, the blood-pressure effects observed in man seem to correlate with the effects of α-methyldopa on norepinephrine, which, however, may not be due to decarboxylate inhibition at all. The possibility must also be borne in mind that α-methyl-dopamine, formed in vivo by the decarboxylation of α-methyldopa, could mediate sympathetic blockade through a mechanism similar to that offered for dopamine in the previous section on MAO inhibitors. Clearly, decarboxylase inhibitors cannot be considered categorically as potential hypotensive agents. Only after a careful correlation has been made of basic and clinical results with several decarboxylase inhibitors will this problem be adequately understood and the pharmacological counterparts of alterations in amine metabolism definitely established.

Summary

The principal processes of synthesis and metabolism for aromatic amines have been discussed in terms of their status in essential hypertension and in relation to alterations induced by enzyme inhibitors with hypotensive properties. From a practical standpoint, the clinical use of monoamine oxidase inhibitors and a decarboxylase inhibitor (α-methyldopa) approach the achievement of medical sympathectomy without prohibitive side effects. From a basic standpoint, use of these inhibitors as biochemical tools affords a new perspective into connections between aromatic amine metabolism and blood-pressure regulation. A combined pharmacological-biochemical approach in man will be an important phase of future investigations.

Acknowledgment

Permission to discuss unpublished observations in the Laboratory of Clinical Biochemistry (S. Udenfriend, Head) on biochemical effects of α-methyldopa is appreciated. Other data represent the combined efforts of members of the Section of Experimental Therapeutics, including Drs. J. R. Croft, J. A. Gotes, L. Gillespie, Jr., D. Horwitz, and L. Goldberg.

References

Discussion

Dr. Miller: I was troubled by your reasoning on the O-methyl transferase. It seems to me that hypertension is so specifically a disease of the vascular system that it is extremely dangerous to relate data derived from the total body to this particular system. Also, I would question any data compared with a single normal.

Dr. Sjoerdsma: I agree with you on both points. It represents the best we have been able to accomplish to date; in the latter instance the data are highly preliminary.

Dr. Hoobler: You mentioned that, after infusion of catecholamines, end products could be detected in the urine. Since you found no increased excretion of these substances in hypertension, you speculate that excessive local release of norepinephrine at sympathetic nerve endings is probably not involved in hypertension. Also, I wonder if you have measured the urinary excretion of the metanephrines after physiological stimuli, such as the upright posture, which normally lead to increased local release of catecholamines, and, if an increased excretion was found on standing, whether it could be prevented by your metabolic inhibitors? Secondly, regarding diurnal variation in excretion of catecholamine end products, does this excretion vary with the day or night? Many of us are interested in the increased level of sympathetic tone apparently prevailing in the evening as compared to the morning; this is indicated by decreased orthostatic hypotension in the evenings when patients are under continuous sympathetic blockade with guanethidine.

Dr. Sjoerdsma: I interpret your first question as asking whether or not these agents alter the releasability of norepinephrine from nerve endings. This is a difficult problem to study in man, I think. We have not studied the effects of posture on diurnal variations, which you mentioned might be of interest. Our approach has been to attempt to study releasability through injection of agents such as tyramine on the premise that, if a significant release could be obtained with tyramine, it would be possible to determine whether this releasability was altered by substances such as α-methyldopa or a monoamine oxidase inhibitor. The only good releaser in patients is reserpine, but I am hesitant about injecting a large dose of reserpine into a patient receiving a monoamine oxidase inhibitor or decarboxylase inhibitor, particularly the latter. I am not sure about any precise correlation of diurnal variation with the effects of these compounds on blood pressure. With monoamine oxidase inhibitors the period of lowest blood pressure occurs when the patient rises in the morning. Otherwise, there is a rather stable change in pressure with minor variation.

Dr. Mendlowitz: We were among those who were stimulated by Dr. Sjoerdsma's and Dr. Axelrod's work to think that there might be some enzymatic defect in essential hypertension. I don't believe this should be completely written off for several reasons. From work in our own laboratory, we thought that reactivity to vasoactive substances was one of the important means whereby people with hypertension constricted their blood vessels and raised their blood pressure. There were three areas to be investigated in this respect. One was the nature of amine metabolism. We came to conclusions similar to those of Dr. Sjoerdsma, but we believe that storage and rate of degradation have to be investigated further. Recently, in association with Dr. Wolf, we have been giving radioactively tagged vasoactive substances, notably angiotensin, intravenously to normotensive and hypertensive subjects and have found a definite decrease in the turnover of angiotensin in all hypertensive individuals as compared with normotensive controls. This is much easier with angiotensin than with norepinephrine because angiotensin has a long half-life in the blood. I am not talking about the half-life of the radioactive label but the half-life of angiotensin. Norepinephrine, on the other hand, is more quickly dissipated in the blood. The metabolism of these vasoactive substances deserves very careful...
ful and very pains-taking evaluation. If such studies should be negative or only partially productive, it would be necessary to turn to the area of muscle metabolism itself.

Dr. Sjoerdsma: I was trying to emphasize the best that we can do at the level of the intact human. The fact that excretion of the methoxy metabolites seems to be similar in both hypertensive and normotensive individuals is suggestive, in itself, that there is no marked defect in catecholamine metabolism in hypertension. The fact that the metanephrines are so much lower in proportion to the MOMA in normal and hypertensive individuals than after the infusion of norepinephrine suggests that monoamine oxidase may be the primary means of inactivation of norepinephrine formed at nerve endings.

Dr. Lee: These drugs that combat powerful vasoconstrictors may do something in addition to altering the blood pressure. Some manifestations of hypertensive disease may not be related directly to blood-pressure level but rather to vasospasm and interference with peripheral blood flow. Therefore, it is important to devote some attention to the peripheral vessels themselves and not concentrate solely on what monoamine oxidase and decarboxylase inhibitors do as antihypertensives. What do they do as antispasmodics in various vascular fields? Secondly, carboxylases are of widespread importance. In these 40 people who have been studied for up to a year, what has happened to their livers and kidneys and their ability to handle a glucose load?

Dr. Sjoerdsma: Most of our patients are living and well. I can answer to that extent. I am concerned primarily with the monoamine oxidase inhibitors. I don’t think we are producing as extensive a decarboxylase blockade in man as we are monoamine oxidase blockade. One problem that has arisen is the development of febrile reactions in two patients. These came early in treatment. In one case it was associated with a cholestatic type of liver reaction that disappeared within a few days when the drug was stopped and reappeared when the drug was given again. So far, there is no reason to relate this to decarboxylase inhibition, since other drugs that don’t block decarboxylase will do the same thing. We also have had some mental depression in three patients during treatment. Two of them had had depressive reactions under previous reserpine therapy. Again, the effect disappeared rather promptly on discontinuing treatment.

The point I wanted to make here is that little or no hesitancy attends the use of many drugs that are undoubtedly inhibiting enzymes—only we don’t know which enzymes—so, simply the fact that we know which enzymes are blocked by these drugs should not halt further therapeutic evaluation.

Dr. Wakerlin: I wonder if you have tested the effect of monoamine oxidase inhibitors in sympathectomized patients. This might help distinguish central from peripheral influences.

Dr. Sjoerdsma: I am sorry but we have not done that.

Dr. Wood: You presented your data on the urinary catecholamines in hypertensives from the point of view of whether or not they were elevated. Another possibility might be a less active sympathetic nervous system in the hypertensive patient in the face of, let’s say, the angiotensin pressor system. Is there any evidence for that?

Dr. Sjoerdsma: I alluded briefly to it. The only chemical evidence I am aware of is that of von Euler et al. (1957). They found what they thought to be a significantly lower norepinephrine excretion in a hypertensive group than in a normal group during daytime hours, with equilibration at night when the sympathetic nervous system was relatively inactive.
Relationships Between Alterations in Amine Metabolism and Blood Pressure

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