Variations in Catecholamine Metabolism Among Schizophrenics

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Introduction

Schizophrenia has remained a perplexing and baffling disorder throughout human history. Not only in the past but note the criteria of diagnosis remain inconsistent from one clinician to another. Many discrepancies exist: age of onset is a variable, symptoms may change for any given patient from one time until the next, efficacy of pharmaceutical management is not always predictable. The prognosis for a complete and permanent remission of the behavioral characteristics of schizophrenia is frustratingly poor. Many clinicians hesitate to apply the diagnosis except in a few classical type chronic cases and instead use the term "schizoid" or other non-committal term to avoid the stigma associated with a diagnosis of schizophrenia. The disorder is a manifestational entity which is usually not associated with frank evidence of central nervous system dysfunction.

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The Etiology of Schizophrenia is Unknown

When Eugene Bleuler[1] introduced the term "schizophrenia" into the vocabulary to distinguish a particular set of behavioral characteristics from those of other defined psychoses, he did not assert that this grouping of various symptoms constituted a syndrome of one specific etiology. His work directed attention away from the prior search for an unknown metabolic disorder believed to terminate as dementia praecox.

Recently, Manfred Bleuler[2] reported a longitudinal study in which he found seven different patterns of onset manifestations of schizophrenia which he attributed to an interaction of genetic potential and environmental influence. He did not support the hypothesis of specific gene mutation as a basis for the disorder but considered the entire genetic milleau as contributory to the disorder.

An alternative to this hypothesis would be the proposal that schizophrenia may comprise a collection of disorders with different etiologies of particular genetic origin which interacting with the environment terminate as a distinct behavioral pattern.

The Methodology of the Study

The selection of the schizophrenics studied

here was based on psychiatric criteria of Psychopathology although the methodology of the investigation is biochemical. Many biochemical studies of the recent past have been adequately reported and have been effectively reviewed (Kety[3], Rin-kel[4], and Schildkraut and Kety[5]). None of the previous biochemical studies has succeeded in clearly identifying specific subtypes of schizophrenia. Some very promising leads to further investigation have been provided from research programs which evaluated some of the metabolic aspects of the biologically active amines obtained from the body fluids of schizophrenics (Carlson, et al.[6], Glowinski and Axelrod[7], and McGeer, et al.[8]).

Catecholamines Metabolism and Stress

I have previously proposed (Palm[9]) the rational for determining the effectiveness of the enzymes involved in the deactivation of the sympathetic system neurohormones, norepinephrine (noradrenaline) and epinephrine (adrenaline) as they may relate to possible metabolic faults associated with schizophrenia.

These catecholamines are released from the adrenal medulla cells and from peripheral sympathetic nervous system cells in response to stress. The normal action of these hormones is well understood as being the means by which the various systems of the body are adjusted to stress. The mobilization of the catecholamines from the cellular stores is the same for stress of either psychological or physiological origin.

Some of the mobilized catecholamines is reabsorbed by the cells from which it was released and stored in granules within these cells for mobilization at a later time. Some of the catecholamines are filtered from the blood as it passes through the kidneys and are excreted in an unmetabolized form either as the unmodified molecules or in conjunction with other products in the urine.

The catecholamines which initiate the activities of other cells are biologically deactivated by enzymatic action and their end products are excreted in the urine. The proportions of the various excreted products can be used to estimate the envivo deactivation by the various enzymatic routes.

The Pathways of the Catecholamines

Axelrod[1011], von Euler[12], Hagen[13], and Spector, et al.[14] have demonstrated the normal pathways for the deactivation of the catecholamines (Fig. 1). The most common pathway is the methylation by *COMT (catechol O-methyl transferase)* to form norme-tanephrine (normetadrenaline) and meta-nephrine (metadrenaline). These products are then usually oxidatively deaminated by *MAO (monoamine oxidase)* to form MHMAL (3 methoxy 4 hydroxymandelic aldehyde).

This intermediate product is then normally oxidized by *ADH (aldehyde dehydrogenase)* to VMA (vanillyl mandelic acid, 3 methoxy 4 hydroxy mandelic acid). This most common terminal product of catecholamine deactivation has no biological activity and is excreted in the urine.

If the aldehyde (MHMAL) is reduced by the enzyme *AR (aldehyde reductase)* rather than oxidized to VMA by *ADH*, the terminal product is MHPG (3 methoxy 4 hydroxyphenyl glycol). A smaller portion of the catecholamines is initially deaminated by the *MAO* to DHMAL (3,4 dihydroxymandelic aldehyde) and then usually oxidized to DHMA (3,4 dihydroxymandelic acid) but can be reduced by AR to DHPG (3,4 dihydroxyphenyl glycol). Both the DHMA and DHPG should be considered as intermediate compounds which can be excreted or they in turn can be methylated by *COMT* to the terminal products VMA and MHPG.

Other related compounds are also enzy-

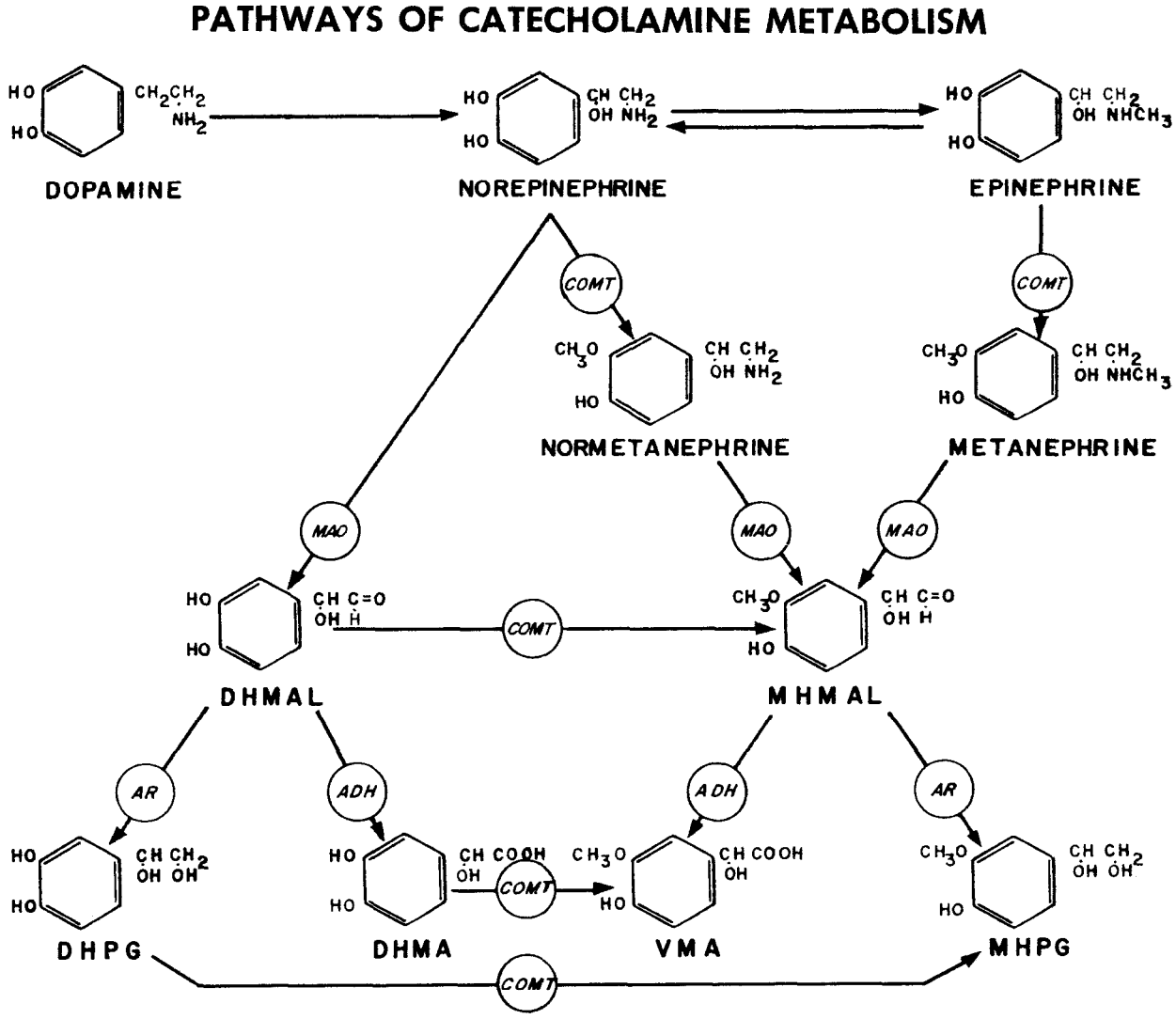

Fig. 1. Enzymes which catalyse the reactions are shown within the small circles. Abbreviations: *COMT* – catechol O-methyl transferase, *MAO* – monoamine oxidase, *AR* – aldehyde reductase, *ADH* – aldehyde dehydrogenase, DHMAL – 3,4 dihydroxymandelic aldehyde, MHMAL – 3 methoxy 4 hydroxymandelic aldehyde, DHPG – 3,4 dihydroxyphenyl glycol, MHPG – 3 methoxy 4 hydroxyphenyl glycol, DHMA – 3,4 dihydroxymandelic acid, VMA – vanillyl mandelic acid (3 methoxy 4 hydroxymandelic acid). See text for explanation.

matically modifiable by *COMT, ADH, AR* and *MAO* (Fig. 2). Dopamine can be directly oxidized with the loss of the amino group by *MAO* to DHPAL (3,4 dihydroxyphenyl acetaldehyde) which then in turn is oxidized by *ADH* to DHPAA (3,4 dihydroxyphenyl acetic acid). This intermediate product is normally methylated by *COMT* and then excreted as HVA (homo-vanillic acid) but can be oxidized to DHMA. DHMA is usually methylated by *COMT* to VMA but can be oxidized by any of several oxidizing agents to DHBA (3,4 dihydroxybenzoic acid) which then in turn can be methylated by *COMT* to VA (vanillic acid) the normal excretion product of this enzymatic sequence.

Enzyme Deficiency

Several of the enzymes listed above are

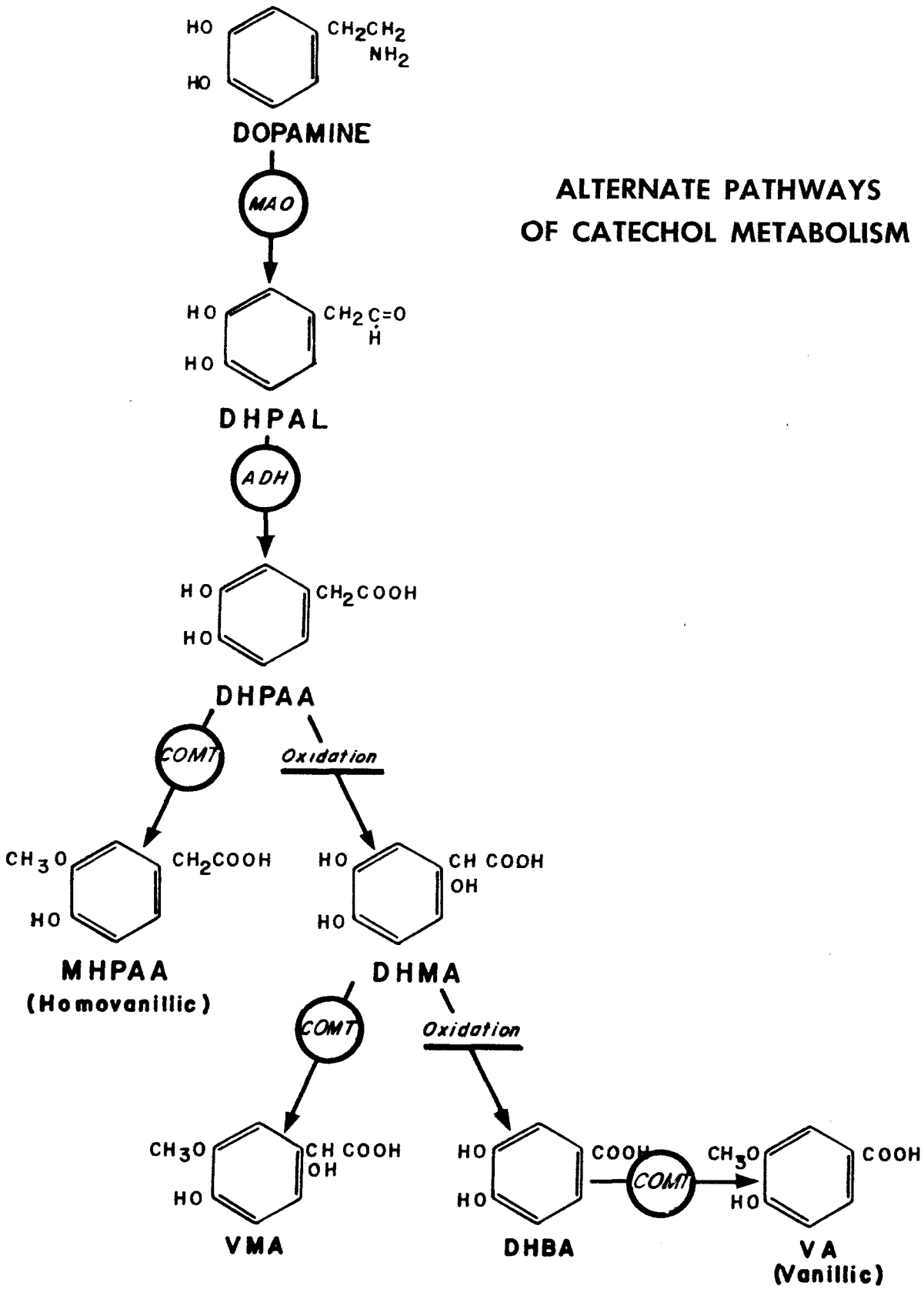

Fig. 2. Enzymes which catalyse the reactions are shown within the small circles. Abbreviations: DHPAL – 3,4 dihydroxyphenyl acetaldehyde, DHPAA – 3,4 dihydroxyphenyl acetic acid, MHPAA – 3 methoxy 4 hydroxyphenyl acetic acid (homovanillic acid) DHMA – 3,4 dihydroxymandelic acid, VMA – 3 methoxy 4 hydroxymandelic acid (vanillyl mandelic acid), DHBA – 3,4 dihydroxybenzoic acid, VA – vanillic acid (3 methoxy 4 hyroxybenzoic acid). Enzymes are: *MAO* – monoamine oxidase, *ADH* – aldehyde dehydrogenase, *COMT* – catechol O-methyl transferase.

common to all of the pathways of deactivation of the catecholamines but whereas *MAO* acts on many kinds of compounds which have the NH_2 (amino group) attached to the molecule and *ADH* and *AR* react with a large variety of aldehydes, the *COMT* acts only or at least primarily on the catechol molecules.

This recitation of the enzymatic pathways clearly demonstrates the normal inherent variability in the deactivation of these "transmitter" substances. A reduction of the normal activity of *COMT* would thus be expected to increase the excretion of the normal intermediate products and to decrease the formation and excretion of the normal terminal products. The relative concentrations of these normal intermediate and normal terminal products in the urine of schizophrenics and a control population serves as the basis for the investigation reported here.

Vanillic acid, homovanillic acid, dihydroxybenzoic acid and other possible products of catecholamine deactivation are also obtained in normal diets so their concentrations are not indicative of enzymatic efficiencies of sympathetic system metabolism alone.

The Amines and Phenolic Acids

Several methods are available for the separation and the quantification of the amines and phenolic acids found in human urine. Most of these methodologies are highly specific for certain of the small molecular weight substances found in urine but are therefore also limited in usefullness for mass screening until particular metabolic anomalies are detected by other research regimen.

A variety of these methodologies have been used here to verify the particular components identified by the mass screening tests used. A modification of the gas/ liquid chromatographic method of Horning et al.,[15] and of Sweeley, et al.,[10] following column fractionation of the urine specimen has provided for a new procedure for the simultaneous separation and quantification of the aromatic acids and amines of interest to this study as well as detecting other urinary components from a small urine sample. The proportions of the various products to each other serves as an indicator of the enzymatic route of catecholamine deactivation and as an indication of the activity of each of the enzymes available for this process.

METHODS AND MATERIALS

The research program was designed to investigate the urinary aromatic acid and methylated catecholamine concentrations of a large group of non-differentiated, institutionalized schizophrenics and from a group of younger acute schizophrenics who were patients of private psychiatrists.

Selection of Subjects

The initial set of urinary phenolic acid and amine records was obtained from morning urine samples from a group of 70 schizophrenic patients who were institutionalized at the Rochester State Hospital, Rochester, Minn. This divergent group included a nearly equal number of males and females of all age groups represented in the hospital. All varieties of clinical expression, physiological condition and length of hospitalization were included. Neither diet nor medication was controlled for the initial screening. Patients with known metabolic disorders were excluded.

The urine chromatograms of the institutionalized schizophrenics were compared with those from a group of healthy, non-schizophrenic, non-institutionalizd persons of the same age and sex distribution as the patient group. Members of the control group had no history of previous psychiatric

pathology and were not known to be related to any schizophrenic persons. Non-schizophrenic siblings of the young, acute schizophrenics were used as a control group.

Extraction of Urine

Morning urine samples were routinely collected. In certain cases 24-hour urine specimens were also collected from some of the schizophrenics as well as from some of the controls. The morning urine samples were collected immediately on the awakening of the subjects. All samples were refrigerated until they were tested.

Several different determinations were made on each sample. A 25 ml. portion of the raw urine was extracted to obtain a record containing the total pyridine soluble fraction of the urinary constituents. A second 25 ml. portion of urine was diluted to 250 ml. and passed through a Bio Rad AG 501-X8 mixed bed resin column. The non-polar constituents of the urine were recovered from the effluent. The column was then washed with 100 ml. of 0.1 M NaCl to elute the phenolic acids and similar compounds. A third fraction was recovered from the mixed bed resin by flushing the column with 1.0 M NaCl.

The method of final extraction was identical for all of the samples. The samples were evaporated to 5 ml. in a rotary evaporator at 60° C. and reduced pressure. A 25 ml. portion of spectro-grade redistilled pyridine was added to this concentrated urine solution and the resulting mixture again evaporated to 2-3 ml. The addition of a second 25 ml. of pyridine caused the precipitation of some of the urine components. The solution was decanted and evaporated to **1.0** ml.

Silation and Chromatography

This pyridine solution of the dehydrated urinary components was then transferred to individual reaction vessels. The compounds were converted to volatile derivatives for gas/liquid chromatographic separation by the addition of 1.0 ml. "BSA" (N, O-bis (trimethylsilyl) acetamide (Pierce Chemical Company, Rockford, Ill.). The samples were held in a water bath at 60° C. for three hours and then chromatographed. The derivatives were separated in an Aerograph 200 Chromatograph employing coiled 5' x 1/8" tubing with both a *5%* SE-30 and a *3%* SE-52 column and flame ionization detection. Most determinations were made with an initial temperature of 125° C. and a 4° C./minute program.

The concentrations of the individual aromatic acids and amines were obtained by determination of the areas under the peaks at specific retention times. Retention data are expressed as methylene unit values (MU) by comparing the retention time for a chromatographic peak with the times obtained for standard hydrocarbons by linear interpolation. The hydrocarbon markers were added to a second chromatogram record. These markers were chosen so that they would not interfere with peaks found on the first record and were standardized so that the hydrocarbon peaks were of the same magnitude as the peaks of the original urinary constituents.

Identification of Constituents

Standards for each of the acids, amines, glycols, sugars and other known urinary components were obtained from commercial supply houses. MU values for each of the products was individually determined and again after their addition to a standard urine sample. Mixtures of the various standard compounds required reaction of each compound individually with the "BSA" and then their subsequent combination, to reduce interactions which occasionally produced unstable complexes if initially mixed

and then reacted with the "BSA" reagent.

Normal urine products which are unrelated to the aromatic acids and amines, e.g. urea, creatinine, hippuric acid, nicotinic acid, nicotinamide, and ascorbic acid, were identified and recorded. The MU of the identified urinary components are given in Table I. A new parameter, the Methyl Transferase Index, which provides an estimate of *COMT* activity was computed for each sample. This index was obtained by dividing the area of the DHMA peak by the sum of the area of the DHMA and VMA peaks (Fig. 3). High *COMT* activity increases VMA excretion and thus gives rise to an index number near zero while a deficiency of *COMT* gives rise to a high (near 1.0) abnormal index number.

TABLE I

METHYLENE UNIT (MU) VALUES FOR URINARY CONSTITUENTS

Compound	*MU Value**
Phenylalanine	16.32
Vanillic acid (VA)	17.63
Homovanillic acid (HVA)	17.70
3,4 Dihydroxyphenylacetic acid (DHPAA)	18.31
3,4 Dihydroxybenzoic (protocatechuic) (DHBA)	18.43
3 Methoxy 4 hydroxyphenyl glycol (MHPG)	18.57
3 Methoxy 4 hydroxymandelic acid (VMA)	18.91
3,4 Dihydroxyphenyl glycol	19.09
Octopamine	19.16
3,4 Dihydroxymandelic acid (DHMA)	19.46
Norepinephrine	19.50
Tyrosine	19.63
Sorbitol	19.78
Ascorbic acid	19.96
Epinephrine	20.41
Metanephrine	20.44
Normetanephrine	20.47
Dopamine	20.97
DOPA	20.31
Tyramine	21.41
5 Hydroxyindolacetic acid (5HIA)	22.45

* MU values calculated by linear interpolation of retention times of compounds and n-hydrocarbon internal standards on *3%* SE-52 column, 125° C. initial with 4° C. per minute temperature rise. Compounds with MU values differing by more than 0.2 can be resolved from total extract others resolved after differential separation on a Bio Rad 501-X8 Mixed Bed Resin.

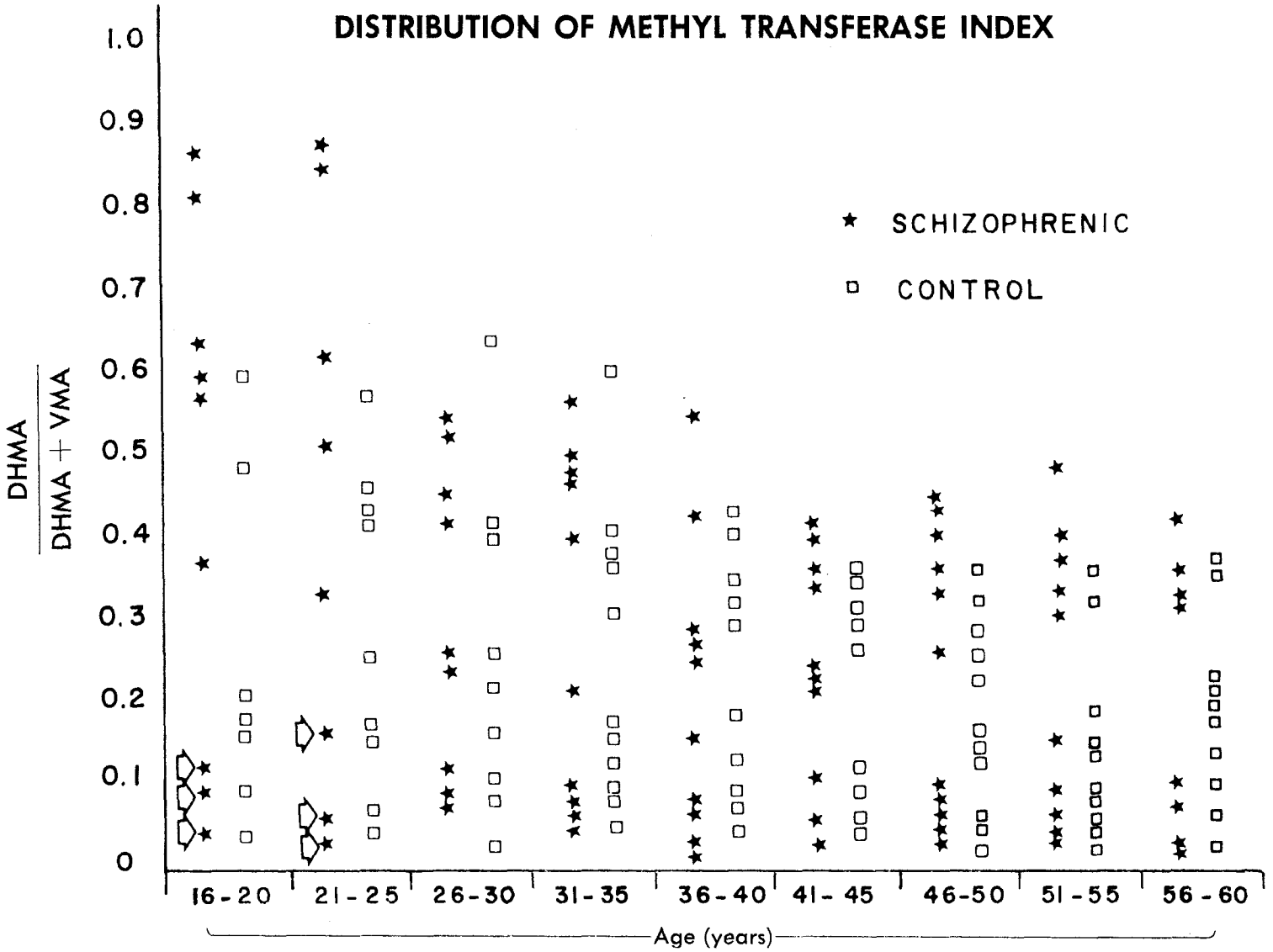

Fig. 3. See text for explanation. Arrows indicate accumulations of all catecholamine and catecholamine products at very high concentrations.

RESULTS AND DISCUSSION

The hypothesis that all schizophrenics are distinguished by a high Methyl Transferase Index number is not supported by this research program. A deficiency of *COMT* activity indicated by an Index Number near 1.0 was not consistently found among the schizophrenics tested. In some, but not in all cases, the gas/liquid chromatograms of the urine extracts clearly distinguished the schizophrenic individuals from the non-schizophrenic controls. In no instance was a high Methyl Transferase Index found in non-schizophrenics.

The Methyl Transferase Index of the schizophrenics was compared with that of the age and sex paired member of the non-schizophrenic control group. The distribution of this measure of *COMT* activity in relationship to the ages of the test subjects is shown in Fig. 3. No sex differences were detected.

Abnormal Methyl Transferase Indexes

Distinctly aberrant Methyl Transferase Indexes were found only among those patients under 25 years of age. Records from many of the older, institutionalized schizophrenics were notable in their almost total lack of VMA, DHMA, norepinephrine, normetanephrine, epinephrine and meta-nephrine although the concentrations of other urinary components were nearly the same as that found in the control group of the same age.

The deficiency of the catecholamines and the normal intermediate and terminal products among the older schizophrenics as well as some of the older controls substantially increases the possibility of error in the computation of the DHMA/DHMA + VMA index of *COMT* activity and necessitates a cautious interpretation of this ratio in older subjects.

Nicotinamide and Ascorbic Acid Excretion

The urinary excretion of nicotinamide and ascorbic acid among those schizophrenics who were being treated according to the mega vitamin regimen can be assessed by the gas/liquid chromatographic techniques used in this study. The nicotinamide MU shows that this compound does not interfere with the detection of the phenolic acids or catecholamines. The MU value of ascorbic acid is so close to DHMA and norepinephrine that care must be used to prevent their overlap and subsequent loss of accuracy of concentration determination.

Among the schizophrenics under 25 years of age two distinct patterns, both different from the control population, were evident. In four of the 17 records of schizophrenics from this group of acute schizophrenics who were not taking any medication when the urine sample was collected, the concentration of DHMA exceeded that of the VMA by a factor of 5-6X and thus gave ratios of DHMA/DHMA + VMA of 0.81 -0.88. In addition to the preponderance of the DHMA in these individuals, the actual concentration of the DHMA, VMA, norepinephrine and epinephrine in relationship to other urinary components suggests a very high mobilization of the catecholamines while the relative deficiency of VMA probably indicates a deficiency of *COMT* in these persons.

In six other records from this group of young schizophrenics, the concentration of both VMA and DHMA were high in relationship to the other urinary low molecular weight molecules. The relatively high concentration of VMA in these persons leads to low DHMA/DHMA + VMA ratio which is well within the range obtained from the control population yet the records were distinct from those of the controls. The high concentration of all catecholamine deactivation products and the excretion of large amounts of norepinephrine

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and epinephrine indicates a high mobilization of the neurohormones. The concentrations of these products in the six young schizophrenics was greater than had been found in an unpublished previous study of varsity athletes at St. Olaf College, North-field, Minn.

Concentration of Metabolites

It is evident here as well as in the study of the athletes that it is necessary to avoid the pitfall of attempting to establish average or "normal" values for the excretion rate of either the individual unmodified catecholamines or the individual normal intermediate and terminal products.

The unmodified or active catecholamines are lost into the kidney tubules and thence to the urine only when they are in very high concentration in the blood. This time of high concentration occurs only for a relatively short time after the stress has caused the mobilization of the active molecules and before the normal reabsorbtion or enzymatic deactivation has reduced the concentration of these active transmitter compounds.

In the tests on the athletes it was found that if a sample of urine is collected shortly after the stress is applied, the unmodified compounds are prominent in comparison to the normal terminal products. If no sample is collected for several hours after the stress condition has caused the mobilization of the active molecules, the relative concentration of the normal intermediate and normal terminal products increases to several times the concentration of the active products.

Although these considerations can be logically deduced they have usually been ignored by previous investigators who have gone to great lengths to establish the norms for these products. Among the athletes, urine samples were collected just before the game, at the half and at the end of the game or several hours after the game.

When samples were collected just before the game or at the half, another sample was not collected until several hours after the game to reduce the problems of dilution effect. Among the athletes the amount of the initial catecholamine mobilization varied with the amount of stress applied, the physical condition of the subject and a factor which can be called the responsiveness of the subject to the stress. The concentration of the unmodified catechols and the deactivated products in turn varied with the amount of the initial catecholamine mobilization and the length of time during which reabsorbtion and enzymatic deactivation took place.

Catecholamine Deactivation Pathways

A determination of the effectiveness of the various enzymatic deactivation pathways must therefore allow the maximal time between the mobilization of the catecholamines and the collection of the urine sample. Since the sympathetic nervous system is least active during sleep, the mobilization of the catecholamines is lowest during this time. Thus, the concentration of the unmodified compounds is normally minimal in a morning urine sample since sufficient time has allowed the enzymatic conversion reactions to deactivate the products and accumulate the inactive molecules in this urine sample.

The samples collected from the schizophrenics had been taken immediately upon awakening so the high concentration of the catecholamines and the conversion products reflected mobilization of the active molecules during the late evening or during the night. Four of these six schizophrenics have previously had histories of hypoglycemia but blood sugar determinations were not made when the urine samples were collected.

If hypoglycemia and high catecholamine mobilization coexist this may not be the contradiction that initially seems evident. If blood glucose level initiates epinephrine mobilization to stimulate glucose release from cellular glycogen stores the lack of this effect by the epinephrine may maintain the epinephrine mobilization with a hypoglycemic situation. A test for glucose tolerance would not indicate this unusual condition but could serve to reduce the catecholamine mobilization if this feedback is operative in these persons. Whether a high concentration of the active and deactivated products indicates a higher than usual response to stress or a greater than normal stress has not been determined.

Retest of these six schizophrenics a month after the original sample was obtained showed the same high concentrations. The high VMA obtained in these records would require a high *COMT* activity in these persons. A high *COMT* activity gives a low Methyl Transferase Index (indicated by arrows on Fig. 3) and distinguishes these records from the four high Index records of acute schizophrenics.

High Sorbitol Concentrations

A high concentration of sorbitol in conjunction with an unusually high concentration of DHPG and MHPG and a virtual lack of DHMA and VMA distinguished the record of one of the young acute schizophrenics but was also found in the record of his younger sister who had been included in the control group.

The identification of the sorbitol and its verification by co-chromatography and mass spectrometry was accomplished by members of the MAN Program at Oak Ridge National Laboratories. Sorbitol is the end product of the reduction of glucose by *AR*. The mandelic aldehydes are converted to the phenyl glycols by this same enzyme (Fig. 1).

These alcohols—sorbitol, DHPG and MHPG—were found only in the urines of two members of one family although the diet was the same for all members of the household. The younger sister has not been diagnosed as schizophrenic although she has exhibited behavioral problems that were unknown to this investigator when the original samples were collected. Subsequent tests have shown lower sorbitol levels in these two individuals which correlate with lower DHPG and MHPG excretion and decreased behavioral symptoms without an increase in VMA or DHMA.

The presence of MHPG indicates the methylation reaction of *COMT*. The action of *MAO* is required for the formation of DHPG from norepinephrine. The combination of the sorbitol with the phenyl glycols suggest a high *AR* activity while the lack of the DHMA and VMA could be due to a deficiency of *ADH*.

SUMMARY

The urinary excretion of low molecular weight compounds derived from adrenal medullary hormones can be accurately determined and simultaneously compared by gas/liquid chromatography with the excretion of a variety of other urinary constituents. Only a small sample is required. The preparation of the sample is simple and the product obtained is stable under ordinary laboratory conditions. Differences in the concentration of the normal inter-

mediate and normal terminal products of enzymatic deactivation of the sympathetic system neurohormones can be used to estimate the effectiveness of the various enzyme pathways available for the deactivation of these products.

Abnormal Patterns Found in Schizophrenics

The urinary excretion patterns of the majority of the non-differentiated schizophrenics could not be distinguished from those of the control population.

Three varieties of abnormal patterns were found among the schizophrenics which distinguished these records from those of the controls as well as from each other.

In one group of records from young, acute schizophrenics the abundance of excreted norepinephrine and epinephrine and their deactivation products there is good evidence that these individuals respond to stress situations with a higher than normal mobilization of the sympathetic system hormones. Some of these persons have a high concentration of VMA in the urine sample indicating a high *COMT* activity while another group had a deficiency of VMA when compared to a high concentration of DHMA and thus indicates a deficiency of *COMT* in these persons.

Among the older, chronic schizophrenic group a general deficiency of the catecholamines and their metabolic products indicates a lower than usual mobilization of the catecholamines as detected in the morning urine samples. The members of this group had all been institutionalized for extended periods of time. The paucity of catecholamine products may be the result of this pattern of living rather than being a characteristic of chronic schizophrenia.

The detection of a high excretion of sorbitol, DHPG and MHPG with a lack of the phenolic acids, DHMA and VMA may
indicate a deficiency of the normal *ADH* activity accompanied by a high *AR* activity in one young schizophrenic as well as in his younger sister who has also shown some behavioral abnormalities but has not been diagnosed as schizophrenic. This pattern is different from the other schizophrenics tested.

Acute Versus Chronic Schizophrenics

The three types of abnormal excretion patterns found only among the schizophrenics seem to be at opposite ends of two different continua. High catecholamine mobilization was demonstrated in persons with a recent onset of behavioral problems. Low catechol mobilization differentiated a group of chronic schizophrenics with long term histories of behavioral problems.

Two different patterns of enzymatic de-activation of the mobilized catecholamines was found among the young, acute schizophrenics. It is unknown if these patterns of biochemical response to stress remain constant in these persons or if a change occurs from the time of acute manifestations to the time of development of chronic patterns.

Introducing a New Hypothesis in the Biochemical Basis of Schizophrenia

A new hypothesis can be formulated about the biochemical basis of schizophrenia to account for a change in catecholamine mobilization as a function of progressive behavioral changes. In this hypothesis, the biochemical component of schizophrenia would be related to the hy-permobilization of the catecholamines in response to stress and an increasing compensatory mechanism which depresses the stress induced catcholamine mobilization. This homeostatic adjustment could serve to isolate the individual from stress induced responses which characterized the person during the acute stages of the disorder.

CONCLUSIONS

Among the records of the schizophrenics tested in a new gas/liquid chromatographic procedure the abnormal patterns are not consistent with the hypothesis that schizophrenia is a single disorder having a simple biochemical etiology. Three previously unrecognized metabolic abnormalities were found among young, acute schizophrenics.

In the young, acute schizophrenics the abundance of excreted norepinephrine and epinephrine and their deactivation products is good evidence that these individuals respond to stress situations with a higher than normal mobilization of the sympathetic system neurohormones.

Some of these persons excrete large amounts of VMA which would indicate an active system of methylation and thus an active *COMT*.

Another group excretes a preponderance of DHMA which is suggestive of a *COMT* deficiency. One member of the test group as well as his younger sister excrete sorbitol and the DHPG and MHPG with a lack of DHMA and VMA which indicates a high *AR* activity and a low *ADH*.

The identification of particular metabolic disorders which decrease the normal regulation of the sympathetic system response to stress among some schizophrenics but not among non-schizophrenic controls reasserts the consideration of the genetic component which interacting with the environmental stresses terminate as schizophrenia.

Results of the study prompt the hypothesis that schizophrenia *is* a behavioral set which results from an inadequate or inappropriate deactivation of catecholamines which are mobilized by stress conditions of the environment. It may be that the recognized manifestations are the best accommodation available to these persons with a metabolic deficiency which establishes a threshold of toleration of anxiety.

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