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CONCENTRATIONS OF EPINEPHRINE AND NOREPINEPHRINE IN PLASMA AND CEREBROSPINAL FLUID ASSOCIATED WITH MENTAL DISEASE*

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With improvements and advancements in methodology and precision instruments, the search for abnormal concentrations of various chemicals in body fluids and tissues of patients with mental disorders has been intensified. A relationship of (a) the sympathetico-adrenal system and endogenous epinephrine and norepinephrine to (b) emotion and mental disease has been suggested by numerous investigators. 2, 4, 5, 7, 8, 14, 21, 22, 25, 28, 38, 39.

Because of repeated assertion that the reactivity of the sympathetico-adrenal system is altered in some mental disorders, quantitation of the plasma pressor amines seemed appropriate in certain psychiatric conditions. With the fluorometric method of Weil-Malherbe and Bone [42] and the modification devised in our laboratory, [29] it has been possible to quantitate epinephrine and norepinephrine in the plasma of normal subjects and psychiatric patients undergoing several forms of "stress" and treatment. In addition, the pressor amines in cerebrospinal fluid have been estimated in a variety of patients.

From the analysis of plasma extracts by the method of paper chromatography followed by elution and fluorometric quantitation, this fluorometric method appears to be rather specific. However, as we have stated previously, [30] it is probable that plasma contains substances other than epinephrine and norepinephrine which are extracted by the method of Weil-Malherbe and Bone and produce fluorescence that may cause a small error in the quantitation of these pressor amines.

In order to test the accuracy of the method, 16 recovery determinations were made in which known amounts of the substances to be assayed were added to plasma and then estimated as unknowns. For the assay of epinephrine, with a mean concentration of 10.0 μg per liter, the standard deviation of the errors of determination was 1.4, or 14%, measured as a coefficient of variation. For norepinephrine, with a mean concentration of 18.1 μg, the standard deviation of the errors was 4.0, corresponding to a coefficient of variation of 22%. For the assay of total epinephrine-like substance,** as was to be expected, since this analysis

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*A preliminary report of this investigation was presented at the XX International Physiological Congress, Brussels, Belgium, July 30 to August 4, 1956 and appeared in more detail in the A. M. A. Archives of Neurology and Psychiatry. 78:396-412 (Oct.) 1957. This study will also appear in a monograph entitled: Chemical Quantitation of Epinephrine and Norepinephrine in Plasma: A Clinical and Experimental Study - by W. M. Manger, K. G. Wakim and J. L. Bollman (to be published by Charles C. Thomas, Springfield, Illinois).

**"Epinephrine-like substance" signifies the concentration equivalent to the fluorescence in the plasma if it were due entirely to epinephrine. Usually epinephrine and norepinephrine are present in plasma. Since we have found that the fluorescence of norepinephrine is only about one-third that of epinephrine, the epinephrine-like substance is less than the sum of the concentrations of epinephrine and norepinephrine when both are present.

involves fewer technical manipulations, the error was smaller than that for either of the specific constituents; the mean concentration was 15.3 μg and the standard deviation was 1.7, represening a relative error of 11%.

Effect of Mescaline and LSD-25

HISTORICAL BACKGROUND. -- In 1953 Liddell and Well-Malherbe [27] reported the effects of intravenous administration of d-desoxyephedrine hydrochloride (Methedrine), 40 to 60 mg., and d-lysergic acid diethylamide * (LSD-25), 40 to 60 mg., on the mental processes and on the concentration of epinephrine - like substance [27] in the blood of a group of patients with mental disorders. After a brief initial period of relaxation, one of the drugs was administered; thereafter the symptoms and the clinical picture became accentuated. The same recurred when the other drug was administered. In the doses used, Methedrine seemed more effective than LSD-25 in increasing tension, in apparently causing cataleptic phenomena and abreaction and in uncovering delusional material. Also, when Methedrine was given to schizophrenic patients, hallucinations appeared more rapidly than when LSD-25 was used. Insomnia occurred frequently after use of Methedrine but rapid swings of mood, with predominant euphoria, were noted only after the use of LSD-25. Similarities of changes in concentration of epinephrine-like substance were observed after administration of the drugs. For example, after administration of Methedrine the concentration of epinephrine-like substance usually increased promptly and then decreased to less than the control value; later there was a slight secondary increase to more than the control value. Some of the patients who received Methedrine, however, did not give evidence of initial increase in concentration of epinephrine-like substance but, rather, of decrease followed by increase. Both of these patterns of change in concentration were observed after intravenous administration of LSD-25 but, when this drug was used, the changes occurred more rapidly than when Methedrine was given. When LSD-25 was administered orally to three patients, only the initial rise, followed by a fall and a secondary rise in concentration of epinephrine-like substance, was observed. The rate of change in concentration was much more gradual after oral than after intravenous administration. After the use of Methedrine, hyperglycemia was noted only when the concentration of epinephrine-like substance was initially increased; no particularly significant rise in concentration of blood sugar was noted after use of LSD-25.

We were interested in the changes in concentration of plasma pressor amines that follow administration to normal subjects of mescaline and LSD-25, as compared with corresponding changes when the patients who received the drugs had mental disorders. A difference in the pattern of change between these two groups might demonstrate derangement of physiochemical responsiveness of patients with certain mental disorders.

PROCEDURE. -- Samples of venous blood were obtained from fasting, healthy, male volunteers (all physicians) after an initial period of 20 to 30 minutes at rest. Immediately thereafter they were given, orally, either 400 mg. of mescaline or 50 μg. of LSD-25**. Samples again were obtained from the antecubital vein approximately 1/2 hour and 1 and 2 hours after the subjects had received the drugs. For greater accuracy, duplicate determinations of epinephrine-like substance were made of all samples except those drawn 1 hour after administration of the drugs. Both epinephrine and norepinephrine were quantitated in the samples obtained 1 hour after administration of the drugs. Blood pressure and pulse rate were determined repeatedly. The subjects were requested to remain seated during the period of observation when physiologic and electroencephlagrophic changes were recorded. In addition, the reversibility of the induced psychoses by administration of chlorpromazine was

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* Herein also called only lysergic acid diethylamide.

** Neither mescaline nor LSD-25 caused any fluorescence when added in fairly large concentrations to samples of plasma which were then quantitated in the usual way for epinephrine and norepinephrine.

noted and this has been reported by Schwarz and associates. [35] *

Under similar conditions the effect of mescaline, and later of LSD-25, was noted on four psychotic patients, who remained recumbent during the period of observation. The effect of these drugs on depth electrograms of two of these patients has been reported by Schwarz and associates. [36] ** We noted, also, the effect of mescaline and LSD-25 on the concentration of plasma epinephrine-like substance in the dog.

Finally, blood samples from two healthy volunteers who did not receive any medication were obtained at the same intervals of time as those mentioned above and were analyzed for concentration of epinephrine-like substance.

The findings are recorded in tables 1 and 2.

RESULTS: -- The observations on concentration of epinephrine-like substance in the plasma at various intervals of time are graphically represented for mescaline and LSD-25 in figures 1 and 2 respectively. There was no remarkable change in these concentrations in any of the groups studied except in the healthy volunteers 1/2 hour and 2 hours after they had received mescaline. At the half-hour interval, the concentration of epinephrine-like substance in the plasma was greater than the control concentration in nine of the 10 volunteers who received mescaline. The elevation of the mean concentration of epinephrine-like substance 1/2 hour and 2 hours after administration of mescaline was of statistical significance. However, because of the small series, this study should be extended to determine whether a clear-cut difference in this biochemical response to mescaline exists between normal and psychotic subjects.

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* Key to identification of healthy volunteers who received the drugs and who are represented in tables 1 and 2 of this chapter as well as in tables 1 and 2 of the paper by Schwarz and co-workers: [35]

Mescaline Number of subject		LSD-25 Number of subject	
Table 1 Schwarz and co-workers	Table 1 Manger and co-workers	Table 2 Schwarz and co-workers	Table 2 Manger and co-workers
2	1	12	1
4	2	1	2
1	3	2	3
3	4	3	4
5-10	5-10	5-11	5-11

** Key to identification of psychotic patients represented in tables 1 and 2 of this chapter as well as in tables 1 and 2 of the paper by Schwarz and co-workers. [36]

Mescaline Number of subject		LSD-25 Number of Subject	
Table 1 Schwarz and co-workers	Table 1 Manger and co-workers	Table 2 Schwarz and co-workers	Table 2 Manger and co-workers
3	1	3	1
4	2	4	2

In table 3 are recorded the mean, the standard error of the mean, and the standard deviation for the concentration of epinephrine-like substance before (control value) and after administration of mescaline and of LSD-25. Also recorded are similar determinations on the differences between the control concentration of epinephrine-like substance and the concentration 1/2 hour and 1 and 2 hours after administration of mescaline and of LSD-25.

Inspection of table 3 discloses that for the volunteers (normal subjects) who received mescaline, the concentration of epinephrine-like substance in the plasma increased over the control value, whereas there was no increase, and in fact a decrease, in concentration in the plasma of all other subjects given mescaline and in that of all subjects given LSD-25. However, only the rise in plasma concentration of epinephrine-like substance in normal subjects 1/2 hour and 2 hours after administration of mescaline is statistically significant (the mean differences being 3.9 and 3.5 times their standard errors, corresponding to P less than .001).

Both epinephrine and norepinephrine were quantitated in the samples obtained 1 hour after the drugs had been given. No deviation from the concentrations in the plasma of normal subjects was noted.

Effect of Methacholine on Blood Pressure and Plasma Pressor Amines

HISTORICAL BACKGROUND. -- In 1948, Funkenstein and co-workers [10] reported the various types of response of the systolic blood pressure that followed intravenous injection of epinephrine or intramuscular injection of methacholine (Mecholyl) in patients with mental disease and in normal subjects. From their results they divide the responses into seven groups. They claimed that the systolic pressure of 80 per cent of the normal subjects fell only moderately or slightly and that it returned to the preinjection level either promptly or within 25 minutes after intramuscular administration of 10 mg. of methacholine. However, only 20 per cent of the mentally ill gave this type of response. The investigators also stated that the response to electroshock treatment could be predicted more accurately from the response of the blood pressure to administration of methacholine and of epinephrine than from the psychiatric diagnosis. For example, patients with mental disease whose fall in blood pressure was distinct and whose hypotension was prolonged following administration of methacholine--sometimes accompanied by a chill--appeared to respond most favorably to electroshock. After such treatment, improvement took place in the condition of 75 per cent of the patients having a decreased reaction to methacholine and of 90 per cent of those having a decrease in basal blood pressure. The following autonomic changes were noted frequently after electroshock treatment: (1) increased reaction to intravenously administered epinephrine, (2) decreased response to methacholine and (3) decreased basal blood pressure. Funkenstein and collaborators expressed the belief that the over-all effect of electroshock was to lower basal sympathetic tension and increase the reactivity of the sympathetic nervous system to stimulation. Decreased reactivity of the parasympathetic system was often a corollary.

In 1950 the same authors reported that changes noted in the response of their patients to epinephrine and methacholine were not specific but occurred with several types of treatment and spontaneous changes in the psychologic picture. [11] They further claimed that the change in the psychologic condition of the patient seemed to accompany change in the physiologic response. Later, in 1951, they reported that the response of mental patients to electroshock and insulin coma differed; they expressed the belief that testing psychiatric patients with epinephrine and methacholine could furnish information on which to base the choice of treatment. [12] In 1952 these authors reported that their psychiatric patients whose blood pressure was elevated fell into two groups: (1) those whose definite fall in blood pressure following administration of methacholine persisted through 25 minutes and (2) those whose blood pressure

fell only slightly following administration of methacholine, with return to the preinjection level within 25 minutes. [13] The findings suggested that the pronounced and prolonged hypotensive response indicated the presence of an excess of epinephrine in the blood. A slight fall, with rapid restoration of homeostasis, suggested the presence of an excess of norepinephrine.

Gellhorn studied the effects of methacholine on the cat and stated that the larger the dose the more prolonged was the depressor action. He observed that the sympathetic response is evoked by way of the sino-aortic nerves [16] and occurs when the fall in blood pressure is large. [15] From additional studies he concluded that "the degree and particularly the duration of the hypotensive action of mecholyl and the reflexly induced discharges of the sympathetico-adrenal system depend on the hypothalamus." [17] He further stated: "Apparently conditions leading to increased sympathetic discharges of the hypothalamus as the result of electrical or chemical stimulation augment the responsiveness of the sympathetico-adrenal system to mecholyl and lead to a quicker return of the blood pressure and/or an overcompensatory hypertensive phase." [18]

PROCEDURE: -- In view of the findings and hypotheses of the investigators named in the foregoing, we decided to study the effect of intramuscular administration of 10 mg. of methacholine on the concentration of plasma pressor amines of patients with various psychiatric conditions. Twenty-one subjects (all fasting) were studied, and the observations are presented in table 4. For obtaining samples of blood from most of these patients, without repeated venous puncture, an indwelling needle equipped with a stylet was used. Only two of these subjects (17 and 20, table 4) had hypertensive basal blood pressures.

RESULTS: -- The three characteristic types of blood pressure response to administration of methacholine are shown in figure 3. The records are from three different subjects. The response of the normoreactor, following intramuscular administration of 10 mg. of methacholine (Mecholyl), consisted of a drop of the systolic blood pressure, with restoration to basal level within 10 minutes. The response of the hyperreactor was characterized by a drop in blood pressure followed by a rise above basal level.

These are empirical classifications which represented the blood pressure responses of nearly all the subjects observed. One subject, after injection of methacholine, exhibited a slight initial rise in blood pressure, followed within 1 to 2 minutes by a fall in pressure below the basal level and subsequent recovery to the basal level. This type of blood pressure response was not mentioned by Funkenstein and co-workers [10-13] and is not represented by any of our three classifications. Only subject 1 (table 4, normal man, age 34 years) reacted in this manner and, since the subsequent pattern of blood pressure response was of the hyporeactor type, he was classified as a hyporeactor. Of another man, age 37 years (subject 3, table 4), the blood pressure rose immediately and remained high following injection of methacholine; only gradually (after 7 minutes) did the pressure return to the basal level. This latter response was considered hyperreactor in type but atypical. * All subjects salivated excessively and experienced profuse sweating within 1 minute after methacholine had been administered intramuscularly.

* In a series of 100 tests with methacholine, one of our associates (C. W. Baars) encountered this type of immediate paradoxical rise of blood pressure four times in four different patients. All four gave evidence of pronounced anxiety, either as the main symptom of their illness or because it had been precipitated by electroshock or carbon dioxide inhalation treatment. After the anxiety had diminished or disappeared as a result of treatment, the paradoxical rise did not again manifest itself. A further possible explanation of this atypical reaction suggested itself 5 months after it had been observed in subject 3 (table 4) when his already existing symptoms of heat intolerance and fatigue became more distinct, persistent tachycardia developed, and a diagnosis of toxic goiter was made. (There was no anxiety at the time of this methacholine test.) On a repeat test, however, 4 months after treatment with radioactive iodine had resulted in definite clinical improvement and considerable drop in the basal metabolic rate, response was typical of the group with normal reactivity to methacholine.

Table 5 reveals the blood pressure reaction and per cent change in epinephrine-like substance in blood samples secured between the start of the second minute and the end of the third as well as between the start of the fourth minute and the end of the fifth after methacholine had been given intramuscularly. Only one of the 11 psychotic patients and none of the five psychoneurotic patients gave the blood pressure response of a normoreactor. Analysis of the results gave no evidence of change in concentration of plasma pressor amines that was consistent with any special pattern. There was no apparent correlation of the diagnosis with the type of blood pressure reaction to methacholine, and there was no indication that the type of blood pressure response was related to the concentrations of epinephrine and norepinephrine in the plasma.

Effect of Electroshock Treatment on Blood Pressure and Plasma Pressor Amines

HISTORICAL BACKGROUND: -- The effect of electroshock on the concentration of plasma epinephrine and of norepinephrine in man was reported in 1955 by Weil-Malherbe.[40] He also cited observations by others that in various animals electroshock was followed by a rise in blood pressure, hyperglycemia, lymphopenia, eosinopenia (in psychotics and psychoneurotic patients), pupillary dilation, contraction of the nictitating membrane, and depletion of pressor amines in the adrenal medulla. Weil-Malherbe found that without previous medication the application of 90 to 120 volts for 0.4 to 0.5 second caused an increase in both epinephrine and norepinephrine in the plasma of patients. After premedication with hexobarbital sodium (Hexobarbitone), the concentration of both substances became elevated subsequent to the application of electroshock but to a lesser degree than without premedication. The addition of a muscle paralyzant to this preliminary medication did not alter the liberation of pressor amines.

In 1958 Griswold reported that in patients and animals that had not received premedication, electroshock resulted in a transient elevation of both plasma epinephrine and plasma norepinephrine.[20] However, pretreatment with a barbiturate or a ganglionic blocking agent completely prevented an increase in plasma concentration of epinephrine and norepinephrine resulting from electroshock. Griswold also noted that succinylcholine chloride partially inhibited the increase in pressor amines after electric shock.[20]

PROCEDURE: -- We have quantitated the concentration of epinephrine and norepinephrine in samples of blood obtained immediately before electroshock, and as soon after it (within 1 to 2 minutes) as practicable from 12 psychotic patients (table 6). All of these patients were given, intravenously, 4 ml. of 2.5 per cent solution of thiopental (pentothal) sodium and 20 mg. of succinylcholine (anectine) chloride just prior to electroshock to minimize the muscular contractions.

RESULTS: -- The effect of electroshock on plasma pressor amines and blood pressure is graphically represented in figure 4 where the results appear in the same order as in table 6. After electroshock, the plasma pressor amines frequently reached the concentrations that were obtained in the plasma of some patients with pheochromocytoma, renal insufficiency, brain tumor or lymphoma and in the plasma of patients who received epinephrine as medication. It is apparent that electroshock invariably caused an elevation in the concentration of epinephrine, whereas the concentration of norepinephrine increased in the plasma of seven but decreased in the plasma of five patients. The epinephrine-like substance increased in the plasma of all patients except that of patient 4 (table 6), who had a slight decrease owing to the diminution of norepinephrine. The increase in mean concentration of epinephrine-like substance and epinephrine from 1.8 and 0.3 (approx.) respectively to 3.1 and 1.5 mg. per liter of plasma was highly significant statistically. However, though the increase in mean concentration of norepinephrine from 5.4 to 5.9 mg. was not remarkable, yet a significant increase or decrease of norepinephrine occurred in the majority of patients (table 6).

In patients 1 and 2 (table 6) the concentration of epinephrine decreased and the concentration of norepinephrine increased following premedication with thiopental sodium and succinylcholine chloride, a muscle relaxant. Blood samples prior to premedication were not obtained in the remaining patients and therefore the significance of the alterations of concentration of epinephrine and norepinephrine in the plasma of patients 1 and 2 following administration of thiopental and succinylcholine chloride is uncertain. Patient 2 (table 6) was acutely disturbed when the blood sample was obtained just before premedication. The systolic blood pressure of all patients was increased immediately by electroshock, whereas the diastolic response was variable. It is noteworthy that the blood pressure of patients who did not improve clinically invariably changed only very little immediately following electroshock.

Pressor Amines in Cerebrospinal Fluid

HISTORICAL BACKGROUND:-- In 1954 Weil-Malherbe and Liddell first quantitated epinephrine and norepinephrine in cerebrospinal fluid. [43] The concentration of pressor amines was determined in fluid removed at encephalography of nine patients with suspected organic lesions of the brain and of nine male schizophrenic patients, three of whom had undergone leukotomy. The concentration of epinephrine and norepinephrine in cerebrospinal fluid was found to be the same in both groups but lower than in venous plasma.

The ratio of epinephrine to norepinephrine in the cerebrospinal fluid and in plasma was the same in both groups, epinephrine representing 25 per cent of the sum of these pressor amines. However, the plasma concentration of pressor amines was lower in schizophrenic patients than in those who were not schizophrenic. It was concluded that cerebrospinal fluid is not merely an ultrafiltrate of plasma but rather a product of epithelium with specific secretory functions. Weil-Malherbe and Liddell also cited the work done by Walter in 1929, which indicated a decrease in permeability of the blood-brain barrier, as measured by the bromide text, in schizophrenia. Accordingly, they would have expected a decrease in the concentration of pressor amines in the cerebrospinal fluid of schizophrenic patients (if the level of these amines depended on the same mechanism as that measured by the bromide test), especially since the plasma concentrations were lower in schizophrenic patients than in other subjects.

PROCEDURE: -- We quantitated the epinephrine-like substance in the cerebrospinal fluid, obtained by introducing a needle into the cisterna magna, of 22 patients (table 7). * In all of these patients except one with a chronic brain syndrome, the results of routine examination of the cerebrospinal fluid, including cell count, determination of total protein and Wassermann test, were normal. The mean and standard deviation of the mean were determined for each group.

RESULTS: -- The findings indicate that among patients with mental deficiency, the mean concentration is lower than it is in other groups, for instance 0.8 mg. per liter of cerebrospinal fluid for patients with mental deficiency as contrasted with 1.2 mg. for those with personality disorder. However, analysis of the results shows that the differences in concentration of epinephrine-like substance in the cerebrospinal fluid of the five groups studied are not statistically significant in the light of the considerable variability of the values and the small number of patients included.

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* With the method of Weil-Malherbe and Bone, the recovery of epinephrine and norepinephrine from cerebrospinal fluid was found to be about 10 per cent less than that from plasma. A correction for this recovery deficit was made when the concentrations in the cerebrospinal fluid were calculated.

Effect of Chlorpromazine on Plasma Pressor Amines

The plasma pressor amines were quantitated before, and one week after, beginning a course of treatment with chlorpromazine (100 mg. three times per day). One patient, a woman 75 years of age, whose condition was diagnosed as paranoid schizophrenia, was agitated and had delusions of persecution. Prior to treatment, the concentrations of epinephrine-like substance, epinephrine and norepinephrine were 2.7, 0.9, and 6.7 μg. per liter of plasma respectively, whereas after 1 week of treatment the values were 2.0, 0.6 and 5.2 μg. per liter of plasma. Clinical improvement was marked at this time. The second patient, a man 59 years of age, whose condition was diagnosed as schizophrenia of the schizoaffective type, was agitated, depressed and suspicious. Before treatment the plasma concentration of epinephrine-like substance, epinephrine and norepinephrine was 1.4, 0.8 and 2.1 μg. per liter respectively, whereas a week after the end of treatment with chlorpromazine (100 mg. three times a day) the values were 2.5, 0.5 and 7.2 μg. per liter. Treatment caused notable reduction in agitation and anxiety and the man began to sleep and eat more nearly normally. In the plasma of the second patient, the concentration of epinephrine decreased while that of norepinephrine increased.

Intravenous administration of 50 mg. of chlorpromazine hydrochloride to an anesthetized dog was followed in 13 minutes by an increase in concentration of epinephrine from 0.2 μg. to 0.9 μg. and a decrease in norepinephrine from 4.8 μg. to 1.1 μg. per liter of plasma. Some of our colleagues [34] have indicated that the administration of chlorpromazine may increase fluorescent substance in plasma other than the pressor amines. Therefore, quantitation of the plasma pressor amines after the administration of chlorpromazine could result in falsely elevated values for epinephrine or norepinephrine or both. As noted above, the total fluorescent substance in the plasma extract of one of our patients decreased whereas in the second patient it increased after the patient had received moderately large doses of chlorpromazine orally. There was a slight decrease in the total fluorescent substance in the plasma extract of a dog after intravenous administration of chlorpromazine. We have not yet determined whether chlorpromazine interfers with the analytical procedure employed in the method of Weil-Malherbe and Bone (or modifications) or whether it alters the plasma concentrations of catecholamines or both.

Lehmann and Hanrahan[26] and other investigators have noted that chlorpromazine selectively inhibits drive and causes mentally disturbed patients to become more tractable without interfering with the higher psychic functions. This drug is also known to have a mild adrenergic blocking action; it reverses the vasopressor activity of small doses of epinephrine and also may have antiacetylcholine properties. However, the exact mechanism of action of chlorpromazine is poorly understood. It has been suggested that it lowers the requirement for cellular oxygen; cortical metabolism apparently is little affected but the reticular substance and possibly the function of the hypothalamus may be altered by chlorpromazine.

Adrenochrome and Mental Disease

Adrenochrome can be prepared by the oxidation of epinephrine as indicated in figure 5. Whether such a reaction occurs in man is uncertain. The presence of adrenochrome in the human body has not been established. Bacq [1] reviewed the subject and cited the work of Wajzer, which indicates that the adrenalin-adrenochrome system is present in mammalian skeletal muscle. In 1954, Hoffer and co-workers [24] reported that adrenochrome given intravenously causes normal subjects to become overactive and to lack judgment and insight or to become deeply depressed for days. Symptoms appear more insidiously and the effects last longer than those from mescaline or lysergic acid diethylamide (LSD-25). Alterations in the electroencephalogram also occur following intravenous administration of adrenochrome. Hoffer and co-workers pointed out the similarity in the structural formula of adrenochrome and some of the hallucinogens such as mescaline and lysergic acid diethylamide (fig. 6).

Furthermore, because of the possible occurrence of adrenochrome in the body, Hoffer and co-workers expressed the view that, in increased concentrations, it could account for symptoms of schizophrenia. They speculated that if deamination of epinephrine by amine oxidase and esterification by sulfoesterase are blocked, then epinephrine may be converted into adrenochrome by phenolase. Hoffer and co-workers reported evidence suggesting that adrenochrome could cross the blood-brain barrier whereas epinephrine could not.

Since the discovery of adrenochrome in 1937, by Green and Richter [19] several investigators have [32] indicated that this substance lacks sympathomimetic activity. We have noted that large doses of adrenochrome given intravenously cause rapid hypotension in the dog.

Martin [32] mentioned that Green and Richter found adrenochrome was a hydrogen carrier. He stated that whereas adrenochrome is pharmacologically inactive, yet it is not biochemically so. He suggested that much of the action of this compound is attributable to its property of reversible oxidation of sulfhydryl groups. The ability of adrenochrome to inhibit enzymes of the glycolytic cycle, such as hexokinase and phosphohexokinase [32, 33] may account for its antimitotic activity reported by Bacq [1] and Bullough. [3] Hoffer [23] claimed to have demonstrated antimitotic activity in the blood of many patients with mental disease; however, this particular finding awaits further investigation.

We also have been interested in the relationship of adrenochrome to mental disease. Unfortunately the procedure of extraction of pressor amines used in the method of Weil-Malherbe and Bone does not extract adrenochrome* which has been added to plasma. Therefore unless sufficiently large amounts of adrenochrome were present actually to contaminate the alumina column used in the extraction procedure for pressor amines, fluorescence would not result from the presence of adrenochrome in plasma. Of course, the properties of this substance in the body, if it is produced endogenously, may differ in some manner from synthetic adrenochrome.) Consequently, the finding of normal concentrations of epinephrine and norepinephrine in the plasma of patients with various psychiatric conditions does not refute the suggestion of Hoffer and co-workers; namely, that excess concentrations of adrenochrome may account for some of the symptoms in schizophrenia. Also, we do not feel that the absence of prominent schizophrenic symptoms in cases of pheochromocytoma is necessarily a strong point against the concept of Hoffer and co-workers, since degradation of epinephrine and norepinephrine may occur through various metabolic pathways without conversion to the respective quinones. Accordingly, the existence of excess quantities of epinephrine and norepinephrin in the body may not be accompanied by excess concentrations of adrenochrome. On the other hand, if some alteration in the metabolism of pressor amines occurred, so that diversion to adrenochrome constituted the main pathway of degradation, then normal concentrations of the pressor amines might result in excess concentrations of adrenochrome.

Serotonin and Mental Disease

In 1954 Wooley and Shaw stated that certain mental processes are probably mediated through the action of serotonin. [44] These authors suggested that the mechanism of action of lysergic acid diethylamide (LSD-25) may be by way of its antagonism to serotonin. In consequence of such an antagonism, deficiency of serotonin available for metabolic activity in the brain might result in mental symptoms. There is a basic structural resemblance of epinephrine, amphetamine, mescaline (trimethoxyphenyl-ethylamine), lysergic acid diethylamide, adrenochrome and serotonin (fig. &). The indole structure is present in the latter three substances and this structure probably can be formed rather easily from epinephrine, amphetamine and mescaline.

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*Obtained through the courtesy of Dr. Abram Hoffer and prepared by Dr. D. E. Hutcheon.

Marrazzi and Hart have found that adrenergic synaptic transmission is present and capable of operating in the brain of the cat. [31] These investigators expressed the belief that, to produce cerebral action when given intravenously, serotonin must pass the blood-brain barrier. They have indicated that serotonin and lysergic acid diethylamide (LSD-25) have qualitatively the same synaptic inhibitory action as mescaline and epinephrine. They pointed out that the interpretation of hallucinations as stimulatory phenomena rather than as consequences of inhibition was not illogical, since synaptic inhibition could result in release from normal restraining influence with subsequent stimulation. They further stated "a disturbance of adrenergic or related cerebral neurohumoral mechanisms appears to be implicated in the actions of the hallucinogens studied." [31] They suggested that perhaps an imbalance between adrenergic inhibition and cholinergic excitation exists as an underlying mechanism in mental disturbance.

More recently Woolley and Shaw [45] have studied the effects of antiserotonins in hypertension and have indicated that serotonin may be causally related to essential hypertension. This is an interesting concept, yet in patients who have carcinoid tumors and hyperserotonemia (occurring spontaneously or induced by a provocative histamine test) we have noted that there may be no mental disturbance, no hypertension and no abnormality in the concentration of plasma pressor amines. [6] These facts, of course, do not refute the concept that mental disturbance may be related to a deficiency of serotonin. The role of serotonin awaits further elucidation.

The method of Weil-Malherbe and Bone, used to extract pressor amines, does not extract serotonin from plasma and therefore the presence of serotonin does not interfere with the quantitation of epinephrine and norepinephrine. It is noteworthy, however, that both serotonin and adrenochrome fluoresce when condensed with ethylenediamine. This may be of value in developing methods for quantitating these substances chemically. It is also important to realize that erroneous quantitations of epinephrine and norepinephrine will occur if solutions containing significant quantities of adrenochrome or serotonin, or both, are analyzed without preliminary adsorption with alumina.

Comment

Effect of Mescaline and LSD-25. -- The significance of the increase in the mean concentration of epinephrine-like substance in the plasma of normal subjects 1/2 hour and 2 hours after oral administration of mescaline is uncertain (table 1). It is tempting to speculate whether some of the symptoms which the drug produced in the subjects could have been related to an aberration in metabolism of pressor amines. The fact that increase in the man concentration of epinephrine-like substance did not occur in the plasma of four patients with mental disease (table 1) after administration of mescaline suggests that a difference may exist between the physiochemical responsiveness of some psychiatric patients and normal subjects.

Effect of Methacholine on Blood Pressure and Plasma Pressor Amines. -- It is apparent that 10 mg. of methacholine given intramuscularly did not significantly alter the concentration of epinephrine-like substance (table 4). This was not surprising since the hypotension following administration of this drug is usually slight and apparently is not adequate to initiate a strong sympathetico-adrenal discharge in order to establish hemeostasis. It will be recalled that Gellhorn's observations on the release of pressor substance after administration of methacholine were made in the cat, and he indicated that pressor substance was liberated after a "considerable" drop in blood pressure. [15] In the presence of marked hypotension it has been found by chemical quantitation that there may be considerable liberation of pressor amines. It is also known that acetylcholine and some related substances can cause liberation of these amines. [9, 37] The dose of methacholine given to our subjects may have been too small to cause significant secretion of pressor amines by the sympathetico-adrenal system. Also it is possible that liberation of a small amount of pressor substance from

sympathetic nerve terminals may have occurred within the tissues where it was almost entirely destroyed, with little or none reaching the blood.

We have not found any evidence to support the concepts expressed by Funkenstein and co-workers, or by Gellhorn, that the methacholine test is a measure of sympathetico-adrenal activity. At least the results of this test as described for man could not be correlated with the concentration of plasma pressor amines in this small series.

Effect of Electroshock on Blood Pressure and Plasma Pressor Amines. -- It had been hoped that the responsiveness of the sympathetico-adrenal system to electroshock (as reflected by the increase in plasma pressor amines) might be used as a prognostic or therapeutic guide. It is evident that the quantity of pressor amines liberated, or the blood pressure response, following electroshock could not be correlated with the clinical state of the patient or with the severity of muscular contractions at the time of treatment (table 6). However, whether any information of prognostic or therapeutic value can be gained from quantitating plasma pressor amines in psychotic patients undergoing electroshock treatment cannot be conclusively settled without repeated observations in much larger series of cases.

Pressor Amines in Cerebrospinal Fluid. -- All the mean concentrations of epinephrine-like substance in cerebrospinal fluid were lower than the mean concentrations in plasma of both normal (average of all volunteers) and psychotic subjects (table 7). The finding that the mean concentrations of epinephrine-like substance among patients with mental deficiency are lower than they are in the other groups studied is interesting in view of the report by Weil-Malherbe [41] that the mean concentration of epinephrine is lower in the plasma of patients with other conditions studied. However, quantitation of pressor amines in the cerebrospinal fluid of a larger number of subjects is indicated before any conclusions can be drawn.

Summary

In this investigation, pressor amines were quantitated in venous plasma of healthy volunteers and of patients with mental disease, as well as in cerebrospinal fluid of subjects with various psychiatric conditions, organic disease of the brain or mental deficiency. After control samples of blood had been obtained, 10 healthy volunteers and four psychotic patients in basal state were given 400 mg. of mescaline orally and blood samples were drawn 1/2 hour and 1 and 2 hours thereafter. An identical study was made of 11 healthy volunteers and four psychotic patients after oral administration of 50 mg. of lysergic acid diethylamide (LSD-25). Personality disturbances occurred in all volunteers, yet little change in symptoms was observed in psychotic patients. Remarkable change did not occur in blood pressure or pulse rate of any normal subject or patient. The mean concentration of epinephrine-like substance in the plasma of the healthy volunteers was significantly increased 1/2 hour and 2 hours after administration of mescaline. There was no rise in the concentration of epinephrine-like substance in the plasma of any other subjects given mescaline or lysergic acid diethylamide.

Intramuscular administration of methacholine (10 mg.) to three healthy volunteers and 18 psychiatric patients caused no significant change, from control values, in concentration of epinephrine-like substance in samples obtained at intervals ranging from 1 to 5 minutes after the drug had been administered and after the blood pressure changes and other effects of methacholine were evident.

In the plasma of all 12 patients who were given electroshock treatment, the transient increase in concentration of epinephrine was significant, whereas the concentration of norepinephrine was significantly increased in the plasma of only five. After electroshock, the concentrations of plasma pressor amines frequently were as great as they often are in some pathologic conditions (pheochromocytoma, renal insufficiency, increased intracranial pressure or lymphoma) or when pressor amines are administered experimentally or therapeutically.

Twenty-two patients representing certain neurologic or psychiatric diseases were divided into five diagnostic groups. The mean value for epinephrine-like substance in the cerebrospinal fluid of any group was not greatly different from that of any other group. However, the mean concentrations in the cerebrospinal fluid were slightly lower than the mean concentrations in plasma of other subjects.

Concentrations of pressor amines in the plasma of patients with mental disease were similar to concentrations in the plasma of normal subjects.

Neither medication with chlorpromazine nor hyperserotonemia resulted in abnormal concentrations of plasma pressor amines. (However, some of our associates have reported increased fluorescent substance in the plasma of patients receiving chlorpromazine.) If adrenochrome and serotonin are present in plasma, they are not absorbed by alumina and, therefore, are not detected by the fluorometric method employed.

Table 1

Plasma Epinephrine Like Substance, Blood Pressure (BP), and Pulse Rate (PR) Before (Control) and After Administration of Mescaline

	Prominent symptoms after mescaline*	Control			After 400 mg. of mescaline orally								
					1/2 hour			1 hour			2 hours		
		ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR
Healthy volunteers receiving drug													
1	Expansiveness, floating sensations, very marked visual effects, nausea	2.7	128/82		4.0	110/80		3.7††					
2	Expansiveness and feeling of well being, marked disturbance in body image, synesthesia	1.1	110/78	78	2.2	118/88	53	1.2	112/76	52	1.8	106/72	53
3	Withdrawal, stuporlike, marked visual effects, synesthesia, vomited 25 minutes after drug	1.2	120/88	78	1.8	128/92	80	1.4	122/90	80	1.0	118/88	80
4	State resembling agitated depression with multiple somatization, nausea	1.5	156/108	80	1.0	168/98	76	1.0	152/108	76	1.6	141/98	78
5	Suspiciousness, auditory hallucinations, hyperacusis, synesthesia, nausea	0.8	116/78	68	1.1	122/88	68	0.8	126/89	70	1.2	146/118	64
6	State resembling agitated depression, many autonomic complaints, nausea	0.9	108/70	52	1.7	128/94	56	1.3	138/74	58	1.6	138/80	56
7	Withdrawal, blocking, Neologisms, marked synesthesia, nausea	0.8	96/68	70	1.1	124/90	76	0.8	118/90	76	1.2	130/98	80
8	Suspiciousness, marked body-image disturbance, disfigured body complex, nausea	0.4	105/72	62	1.1	120/85	68	0.4	108/80	72	1.1	108/80	64
9	Simple withdrawal into ''contemplativelike'' state with visions, nausea	1.9	108/78	80	2.8	110/74	80	2.4	108/72	80	2.5	108/74	80
10	Some anxiety, moderate withdrawal, visions, somesthesia, nausea	0.8	118/80	52	1.5	116/86	52	1.0	118/80		0.8	118/83	64
	Mean	1.2	116/80	68.9	1.8	124/88	67.7	1.4	122/84	70.5	1.4	124/88	68.8
Psychotic patients receiving drug													
1	(Catatonic schizophrenia); mescaline facies, waxy flexibility increased	1.6	88/60	68	1.1	84/68	68	1.4	84/58	64	1.3	96/66	68
2	(Psychosis, grand mal epilepsy); mescaline facies, more talkative	2.1	104/72	80	1.9	106/58	84	2.1	104/68	76	1.9	102/60	88
3	(Paranoid schizophrenia); no change	1.7	118/78	76	1.8	124/76	68	2.0	116/80	80	1.7	120/80	84
4	(Simple schizophrenia); no change	2.3	120/52	96	2.1	108/54	88	1.3	122/58	86	1.6	126/54	84
	Mean	1.9	108/66	80.0	1.7	106/64	77.0	1.7	106/66	76.5	1.6	111/65	80.5
Dog receiving drug													
1	Restless, struggling barking, injected conjunctivas, slight ataxia	1.3			1.3			1.6			1.3		
Healthy volunteers not receiving drug													
1		1.6	108/72		1.6	106/74		1.4	118/84		1.6	114/84	
2		1.0	108/70		1.4	102/68		1.3	104/68		1.2	98/64	
	Mean	1.3	108/71		1.5	105/71		1.4	111/76		1.4	106/74	

*Diagnosis prior to drug administration is given in brackets.
†ELS, epinephrine-like substance, μg. per liter of plasma.
††Blood sample drawn 1 1/2 hours after mescaline administered.

Table 2

Plasma Epinephrine-like Substance, Blood Pressure (BP), and Pulse Rate (PR)

Before (Control) and After Administration of LSD-25

	Prominent symptoms after LSD-25*	Control			After 50 mg. of LSD-25 orally								
					1/2 hour			1 hour			2 hours		
		ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR
Healthy volunteers receiving drug													
1	Detached, sense of timelessness	0.9	110/88	80	1.6	115/78		0.8	122/95		1.2	115/98	
2	Contemplative, daydreaming	1.6	106/78	72	0.9	112/72	64	1.5	104/74	64	1.1	108/70	60
3	Silly, facetious, expansive	2.8	104/78	68	2.7	96/64	70	2.2	102/70	76	2.5	106/70	68
4	Silly, inappropriate grinning	1.4	124/88	84	1.7	120/90	72	1.1	126/90	72	1.1	122/82	84
5	Megalomania, neologisms, synesthesia	2.9	112/74	70	2.1	118/70	62	1.0	124/75	66	0.7	120/70	72
6	Uncontrollable laughing, clang association	2.1	108/72	68	2.3	96/78	64		104/70	64	2.3	104/70	78
7	Expansive, singing, joking, floating	1.0	112/82	64	0.9	102/78	68	0.5	100/76	80	0.5	110/80	80
8	Sense of unreality, grinning to self, pronounced visual effects	2.3	98/62	60	2.5	92/60	56	2.4	98/70	56	2.9	110/80	70
9	Ideas of reference, reminiscences, depersonalization	1.7	122/88	80	2.0	138/98	72	2.0	122/94	64	3.0	118/88	64
10	Preoccupied with somatic sensations, "out of contact and unreal"	1.5	104/84	64	1.6	96/66	64	1.5	102/82	60	2.5	108/84	64
11	Uncontrollable laughter, sense of incongruity, visual effects	2.0	118/78	80	1.7	118/80	84	1.2	110/74	72	1.8	118/80	76
	Mean	1.8	111/79	71.8	1.8	109/75	67.6	1.4	110/79	67.4	1.8	113/80	71.6
Psychotic patients receiving drug													
1	(Catatonic schizophrenia); laughed, talked to self, brighter facies	1.6	100/70	62	1.7	100/70	64	2.4	102/68	64	2.0	108/72	74
2	(Psychosis, grand mal); little clinical effect	2.3	104/70	80	1.5	96/64	82	1.5	106/56	78	1.3	112/58	84
3	(Paranoid schizophrenia); slight clinical effect	2.8	110/74	112	2.0	124/74	84	2.0	110/86	84	2.2	128/86	80
4	(Simple schizophrenia); no change	2.6	128/78	100	2.1	126/74	80	1.6	110/70	72	1.7	122/68	72
	Mean	2.3	110/73	88.5	1.8	112/70	77.5	1.9	107/70	73.5	1.8	118/71	77.5
Dog receiving drug													
1	Crying, barking, struggling howling, chewing block of wood, restlessness	1.4			2.0			1.8			2.3		

*Diagnosis prior to drug administration is given in brackets.

†ELS, epinephrine-like substance, μg. per liter of plasma.

Table 3

Statistical Data on Concentration, in μg. per Liter of Plasma, of Epinephrine-like Substance Before (Control) and After-Administration of Mescaline and LSD-25

		Control	Hours after drug administered					
			1/2	1	2	1/2	1	2
						Differences from control		
Mescaline								
10 volunteers	Mean	1.2	1.8	1.4	1.4-	-.62	-.19	-.38-
	SEM*	.21	.30	.30	.17	.16	.12	.11
	SD†	.67	.95	.96	.52	.50	.39	.34
4 psychotics	Mean	1.9	1.7	1.7	1.6	-.20	-.22	-.30
	SEM	.16	.22	.20	.12	.12	.28	.14
	SD	.33	.44	.41	.25	.24	.56	.29
LSD-25								
11 volunteers	Mean	1.8	1.8	1.4	1.8	-.018	-.39	-.055
	SEM	.20	.17	.18	.27	.14	.18	.28
	SD	.66	.58	.60	.90	.45	.60	.93
4 psychotics	Mean	2.3	1.8	1.9	1 8	-.50	-.45	-.52
	SEM	.26	.14	.20	.20	.21	.42	.32
	SD	.53	.28	.41	.39	.42	.84	.64

*SEM, standard error of mean.

†SD, standard deviation.

Calculations based on 9 volunteers with mean for control values of 1.0

Table 4

Plasma Pressor Amines and Blood Pressure Response

After Intramuscular Administration of 10 Mg. of Methacholine

Subject*	Age, sex	Diagnosis and prominent symptoms	Reaction†	Pressor amines, μg. per liter of plasma S	Before methacholine	Minutes after methacholine‖ 1-3	3-5	5-10	Six-month follow-up¶
1	34 M	(Normal); none	HO	ELS	1.3	1.9	1.9		Normal
				E	0.1	0.0	0.5		
				N	4.5	7.0	5.2		
2	32 M	(Normal); none	N	ELS	2.4	1 7	1.9		Normal
				E	0.0	0.3	0.0		
				N	8.8	5.1	7.0		
3	37 M	(Normal? thyrotoxicosis?); mild heat intolerance	HR	ELS	3 0	2.3	1.9		Found to be hyperthyroid
				E	1.3	1.1	1.3		
				N	6.2	4.3	2.3		
4	38 M	(Personality disorder); sexual deviation	N	ELS	0.8	0.9			Tuberculosis suspect
				E	0.0	0.1			
				N	2.9	2.8			
5	20 M	(Personality disorder); none	HR	ELS	1.1	1.8	1.8		Condition unchanged
				E	1.0	1.4	1.8		
				N	0.4	1.5	0.0		
6	35 M	(Reactive depression); tense, insecure, deep fear and guilt, takes recourse to alcohol	HO	ELS	1.4	1.8	1.0	1.7	No response to therapy: CO_2, chlorpromazine, reserpine, or EST
7	52 M	(Obsessive, compulsive); anxious, depressed, suicidal, groaning	HO (N)	ELS	2.0	1.8	2.6	1.6	Greatly improved by 31 EST and chlorpromazine
8	47 F	(Reactive depression); anorexia, fearful, insomnia, panics, depressed, choking, somatic complaints	HO	ELS	1.0	1.1	1.2		Slight improvement with 14 EST, signed out against advice, fearful of treatment
				E	0.0	0.2	0.3		
				N	3.7	3.2	3.5		
9	50 M	(Psychophysiologic gastrointestinal reaction); nervous, upset, worried, somatic complaints	HR	ELS	2.0	1.5	1.5		Mild improvement after 14 EST
				E	0.0	0.7	0.1		
				N	7.3	2.9	5.1		
10	46 M	(Reactive depression); anorexia, suicidal ideas	HR	ELS	1.3	0.8			Complete recovery after 11 EST
11	19 M	(Schizophrenia, chronic undiff. type); withdrawal, hypoactive, depressed	HO	ELS	1.7	1.8	1.5	1.3	Moderate improvement after 12 EST
12	40 M	(Schizophrenia, paranoid); bizarre behavior, auditory hallucinations, neglects self, suicidal	HO	ELS	1.8	1.4			Moderate improvement after EST
				E	0.0	0.2			
				N	6.6	4.3			
13	61 M	(Reactive depression); agitated, worried, guilt feelings	HO	ELS	1.0	1.2	1.5		Improved after EST
				E	0.0	0.0	0.1		
				N	3.7	4.4	5.2		
14	45 F	(Manic depressive); self accusatory, depressed, almost mute, agitated	HO	ELS	0.7		1.4		Greatly improved on chlorpromazine
				E	0.4		0.1		
				N	1.1		4.9		
		(Condition "better than ever before")	(N)	ELS	(2.6)	(2.8)	(2.8)		
				E	(0.0)	(1.5)	(1.2)		
				N	(9.5)	(4.8)	(5.9)		
15	40 F	(Manic depressive); depressed, mute, somewhat fearful	HO	ELS	1.3	2.0	1.6		Moderate improvement on chlorpromazine, and later rapid improvement on EST
				E	0.9	1.9	0.8		
				N	1.3	0.5	2.6		
			(N)	ELS	(2.1)	(2.1)	(2.7)		
				E	(0.7)	(0.2)	(0.5)		
				N	(5.1)	(7.0)	(8.0)		
16	29 F	(Schizophrenia, chronic undiff. type); depressed, worried, restless, withdrawn, neglects self	N (HR)	ELS	1.0	1.2			No change after 5 EST; later clinical improvement after 21 more EST
17	33 M	(Schizophrenia paranoid); delusional, restless, combative when provoked	HR (HO)	ELS	1.3	1.2	1.4	1.6	Much improvement but not complete recovery after 13 EST
18	36 M	(Schizophrenia, schizoaffective); suicidal, withdrawn, delusions of reference	HR	ELS	1.8	1.7	1.4		Improving after EST
				E	0.0	0.4	0.0		
				N	6.6	4.8	5.1		
19	22 F	(Schizophrenia, acute undiff.); paranoid delusions, auditory hallucinations, ideas of reference	HR (HR, almost N)	ELS	1.5	1.5	1.2	1.4	Very much improved by psychotherapy
20	32 M	(Manic depressive); overactive, restless, silly, talkative	HR	ELS	1.9	1.9		2.2	Improved after chlorpromazine and EST
			(HR, then N)	ELS	(1.1)				
				E	(0.0)				
				N	(4.0)				
21	33 M	(Schizophrenia, paranoid); delusions of persecution	HR	ELS	2.8	2.4	2.5		Only slight improvement after EST
				E	0.5	0.0	0.0		
				N	8.5	8.8	9.2		

*Subjects 1 and 2, normal persons; 3, normal person or one with possible thyrotoxicosis; 4 and 5, patients with personality disorders; 6 through 10, patients with psychoneurosis; 11 through 21, patients with psychosis.
†Diagnosis prior to drug administration is given in brackets.
HO, hyporeactor; N, normoreactor; HR, hyperreactor; ( ), after treatment.
‖ELS, epinephrine-like substance; E, epinephrine; N, norepinephrine.
1 to 3 from start of 2nd minute to end of 3rd. 3 to 5 from start of 4th minute to end of 5th.
5 to 10 from start of 6th minute to end of 10th. ¶ EST, electroshock therapy.

Table 5

Blood Pressure Reaction and Per Cent Change* in Epinephrine-like Substance in Plasma Following Intramuscular Administration of 10 Mg. of Methacholine

Type and condition of reactor	Subjects	Epinephrine-like substance	
		After 1-3 min.	After 3-5 min.
Hyporeactor			
Normal	1	46.2	46.2
Psychoneurosis	3	6.8	9.1
Psychosis	5	10.3†	27.6†
Normoreactor			
Normal	1	-29.2	-20.8
Personality disorder	1	12.5	--
Psychosis	1	20.0	--
Hyperreactor			
Normal? (thyrotoxicosis?)	1	-23.3	-36.7
Personality disorder	1	63.6	63.6
Psychoneurosis	2	-30.3	-25.0
Psychosis	5	- 6.5†	-12.2†

*The mean change from the corresponding control values expressed as per cent of control mean. Only values followed by a dagger (†) are statistically significant since all other values are based on only three or less determinations. 1-3 from start of 2nd minute to end of 3rd; 3-5 from start of 4th minute to end of 5th.

Effect of Electroshock on Blood Pressure and Plasma Pressor Amines in 12 Psychotic Patients*

Patient	Age	Sex	Diagnosis and prominent symptoms†	Physical examination †	Electroshock therapy §	Response to EST at present	Before EST				After EST			
							BP	MLS	Epi.	Nor.	BP	MLS	Epi.	Nor.
1	28	F	(Schizophrenia, paranoid); extremely agitated	Normal (100/68, 76)	8th EST, 500 ma ; 0.5 sec., no twitchings	Remission	100/72	2.0 1.7	1.0 0.8	3.7 6.2	120/80	3.3	1.4	5.6
2	34	F	(Schizophrenia, catatonic); very withdrawn and negativistic	Normal (110/80, 78)	51st EST, 450 ma.; 0.5 sec., grade 3 reaction	Poor, still withdrawn and apprehensive	130/90	1.0 1.2	0.5 0.2	1.7 3.8	125/90	1.8	1.3	5.8
3	40	M	(Schizophrenia, paranoid); somatic delusions, moderate depression	Normal 120/80, 72)	2nd EST, 500 ma., 0.5 sec., grade 3 reaction	Fair, fewer somatic delusions	150/75	1.1	0.2	3.3	160/70	1.0	0.7	3.3
4	55	M	(Psychotic depressive reaction); paces floor, insomnia, weight loss	Normal (160/90, 72)	44th EST, 450 ma.; 0.5 sec., grade 2 reaction	Remission	130/90	3.0	0.1	10.6	140/90	2.5	1.0	5.6
5	45	F	(Schizophrenia, paranoid); ideas of persecution, flat affect	Normal (122/82, 86)	7th EST, 500 ma., 0.5 sec., grade 2 reaction	Fair, less anxiety but still quite paranoid	108/85	1.3	0.4	3.3	125/80	2.6	0.7	7.0
6	60	M	(Schizophrenia, chronic undiff.); mute, silly grin, masturbates	Thrombophlebitis, left leg (142/84, 92)	8th EST, 575 ma., 0.7 sec., grade 4 reaction	Fair to good, not so retarded and repressed, eating and gaining weight	120/75	2.2	0.7	5.4	170/95	4.2	1.3	10.5
7	72	M	(Psychotic depressive reaction)	Normal (134/78, 82)	12th EST, 550 ma., 0.7 sec., grade 1 reaction	Good, less retarded and depressed, no longer stuporous and incontinent of urine	108/58	1.8	0.0	5.9	180/95	2.4	1.1	4.7
8	32	M	(Schizophrenia, chronic undiff.); Halting illogical speech, flat affect, many mannerisms	Thoracic kyphoscoliosis (100/70, 72)	7th EST, 450 ma., 0.6 sec., grade 1 reaction	Poor, no change, same after 18th EST	115/75	1.0	0.0	3.7	118/75	2.0	0.9	4.0
9	30	M	(Schizophrenia, paranoid); delusions of persecution, had threatened to kill mother	Normal (120/80, 76)	20th EST, 550 ma., 0.5 sec., grade 2 reaction	Poor, no change		1.3	0.1	4.3		2.2	1.4	2.8
10	30	M	(Schizophrenia, schizoaffective); attempted suicide by sticking forks in head	Dermatographia (110/76, 82)	1st EST, 500 ma., 0.6 sec.- grade 3 reaction	Fair, less depression	125/80	1.9	0.0	7.0	170/10	3.4	2.5	3.3
11	25	M	(Schizophrenia, paranoid); hears angels talking to him	Marked scoliosis (105/75, 76)	10th EST, 500 ma., 0.6 sec. no twitchings	Remission, rapid response to EST	135/75	1.5	0.2	4.4	140/70	4.6	2.5	7.7
12	31	F	Mild mental deficiency, idiopathic with psychotic reaction, I.Q. 70); believes people trying to kill her, is homicidal--bilateral prefrontal lobotomy 8 years ago without improvement	Prefrontal lobotomy scar (122/88, 78)	7th EST, 500 ma. 0.5 sec., grade 2 reaction	No improvement	135/70	3.2	1.3	7.2	148/69	5.6	3.1	9.9
Mean of total and standard error of mean							124/76	1.8 ±.21	0.2 ±.11	5.4 ±.62	153/80	3.1 ±.35	1.5 ±.23	5.9 ±.74

*Abbreviations: BP, blood pressure. EST, electroshock therapy. MLS, epinephrine-like substance; Epi., epinephrine; Nor., norepinephrine; each in µg. per liter of plasma. Ma., milliamperes.

†Diagnosis prior to electroshock treatment given in brackets. §Blood pressure and pulse rate in parentheses.

‖Grade 1, slight twitching; 2, moderate muscular activity; 3, notable muscular activity; 4, generalized convulsive seizure.

¶Concentrations prior to administration of premedication--all other concentrations were made after 4 ml. of 2.5 per cent solution of thiopental sodium and 20 mg. of succinylcholine chloride had been administered intravenously.

Table 7

Epinephrine-like Substance in Cerebrospinal Fluid (Micrograms per Liter)

Personality disorder (3 patients)	Psycho-neurosis (3 patients)	Psychosis (9 patients)	Chronic brain syndrome*	Mental deficiency (2 patients)**
0.6	0.8	0.7	0.4	0.8†
1.6	1.1	0.8	0.8†	0.9
1.6	1.8	0.9	0.9	
		0.9	1.2	
		0.9	1.8	
		1.0		
		1.2		
		1.3		
		1.7		
Mean ± 1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.1	1.0 ± 0.2	0.8 ± 0.1

*Chronic brain syndrome = organic disease of the brain.

**Cause of mental deficiency unknown.

†Cerebrospinal fluid: 120 mg. of protein per 100 cc. and colloidal gold reaction positive; normal in all other patients.

Number after ± is standard error of mean.

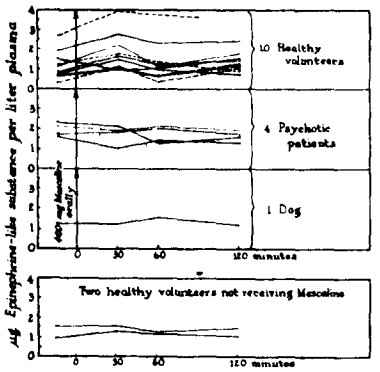


Fig. 1. Effect of mescaline on plasma epinephrine-like substance.

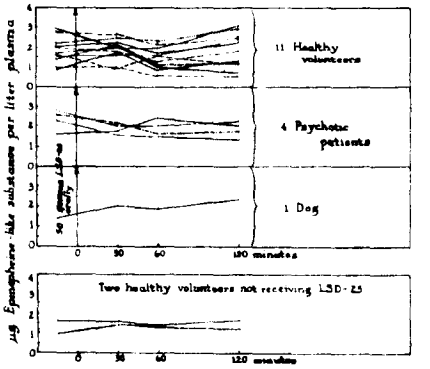


Fig. 2. Effect of lysergic acid diethylamide on plasma epinephrine-like substance.

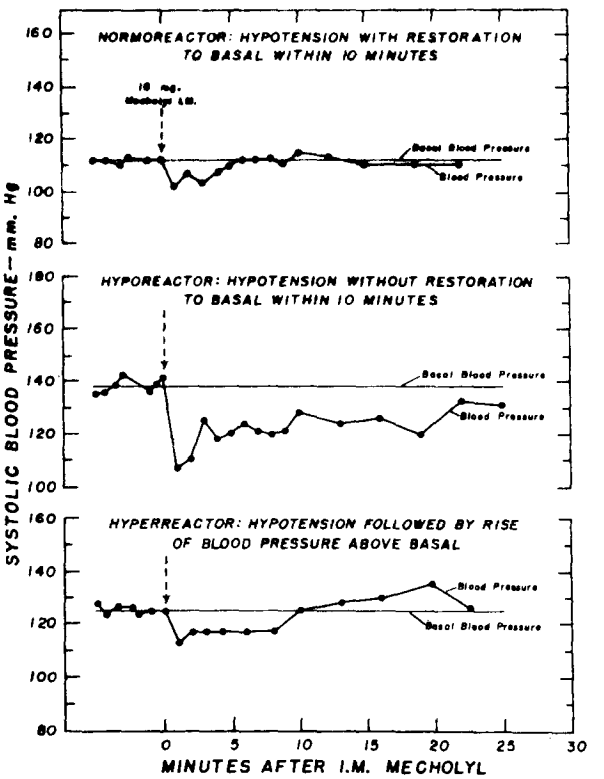


Fig. 3. Types of blood pressure response to administration of methacholine.

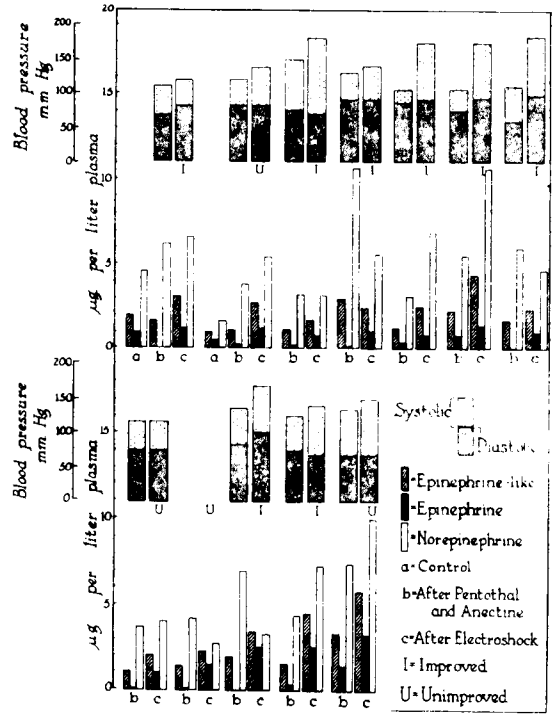
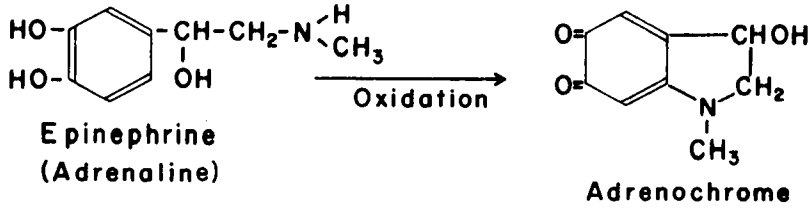


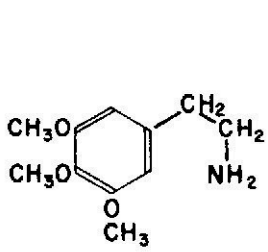
Fig. 4. Effect of electroshock on plasma pressor amines and blood pressure in 12 psychotic patients.



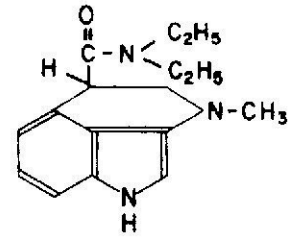
Epinephrine
(Adrenaline)

Adrenochrome

Fig. 5. Oxidation of epinephrine to adrenochrome.

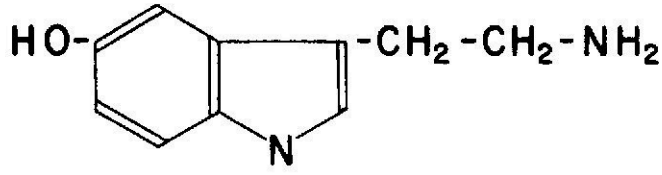


Mescaline
(Trimethoxy-phenyl-ethylamine)



Lysergic Acid Diethylamide
(LSD-25)

Fig. 6. Structural formulas of mescaline and lysergic acid diethylamide.



Serotonin
(5-hydroxytryptamine)

Fig. 7. Structural formula of serotonin.

References

1. Bacq, Z. M. : The Metabolism of Adrenaline. Pharmacol. Rev. (1):1-28, 1949.

2. Bodo, R. C. and Benaglia, A. E. : Hyperglycemia Produced by Sympathin in Emotional Excitement. Am. J. Physiol. 121:738-746 (Mar.) 1938.

3. Bullough, W. S. : Stress and Epidermal Mitotic Activity. I. The Effects of the Adrenal Hormones. J. Endocrinol. 8:265-274 (July) 1952.

4. Cannon, W. B. : Again the James-Lange and the Thalamic Theories of Emotion. Psychol. Rev. 38:281-295 (July) 1931.

5. Dana, C. L. : The Anatomic Seat of the Emotions: A Discussion of the James-Lange Theory. Arch. Neurol. & Psychiat. 6:634-639 (Dec.) 1921.

6. Daugherty, G. W., Manger, W. M., Roth, G. M., Flock, E. V., Childs, D. S., Jr., and Waugh, J. M. : Malignant Carcinoid With Hyperserotonemia Occurring Spontaneously or Induced by Palpation of the Tumor or by Intravenous Histamine: Report of Case. Proc. Staff Meet., Mayo Clin. 30:595-601 (Dec. 14) 1955.

7. Diethelm, Oskar, Fleetwood, M. F. and Milhorat, A. T. : The Predictable Association of Certain Emotions and Biochemical Changes in the Blood. A. Res. Nerv. & Ment. Dis., Proc. (1949) 29:262-278, 1950.

8. Elkes, J. : Discussion. In Tanner, J. M. : Prospects in Psychiatric Research: Proceedings of the Oxford Conference of the Mental Health Research Fund, March 1952. Oxford, Blackwell Scientific Publications, 1953, pp. 126-135.

9. Feldberg, W., Minz, B. and Tsudzimura, H. : The Mechanism of the Nervous Discharge of Adrenaline. J. Physiol. 81:286-304 (June 9) 1934.

10. Funkenstein, D. H., Greenblatt, Milton and Solomon, H. C. : Autonomic Nervous System Changes Following Electric Shock Treatment. J. Nerv. & Ment. Dis. 108:409-422 (Nov.) 1948.

11. Funkenstein, D. H., Greenblatt, Milton and Solomon, H. C. : A Test Which Predicts the Clinical Effects of Electric Shock Treatment on Schizophrenic patients. Am. J. Psychiat. 106:889-901 (June) 1950.

12. Funkenstein, D. H., Greenblatt, Milton and Solomon, H. C. : Autonomic Changes Paralleling Psychologic Changes in Mentally Ill Patients. J. Nerv. & Ment. Dis. 114:1-18 (July) 1951.

13. Funkenstein, D. H., Greenblatt, Milton and Solomon, H. C. : Nor-epinephrine-like and Epineprhine-like Substances in Psychotic and Psychoneurotic Patients. Am. J. Psychiat. 108:652-662 (Mar.) 1952.

14. Gellhorn, Ernst: Physiological Foundations of Neurology and Psychiatry. Minneapolis, University of Minnesota Press, 1953, pp. 327, 328, 357, 359, 422, 430, 431, 432, 466.

15. Ibid., p. 472.

16. Ibid., p. 475.

17. Ibid., p. 476.

18. Ibid., p. 477.

19. Green, D. E. and Richter, Derek: Adrenaline and Adrenochrome. Biochem. J. 31:596-616 (Apr.) 1937.

20. Griswold, R. L.: Plasma Adrenaline and Noradrenaline in Electroshock Therapy in Man and in Rats. J. Appl. Physiol. 12:117-120 (Jan.) 1958.

21. Harris, G. W.: Discussion. In Tanner, J. M.: Prospects in Psychiatric Research: Proceedings of the Oxford Conference of the Mental Health Research Fund, March 1952. Oxford, Blackwell Scientific Publications, 1953, p. 143.

22. Hickam, J. B., Cargill, W. H. and Golden, Abner: Cardiovascular Reactions to Emotional Stimuli; Effect on the Cardiac Output, Arteriovenous Oxygen Difference, Arterial Pressure, and Peripheral Resistance. J. Clin. Invest. 27:290-298 (Mar.) 1948.

23. Hoffer, Abram: Personal communication to the author.

24. Hoffer, Abram, Osmond, Hymphrey and Smythies, John: Schizophrenia: A New Approach. II. Result of a Year's Research. J. Ment. Sc. 100:29-45 (Jan.) 1954.

25. Isquierdo, J. J. and Cannon, W. B.: Studies on the Conditions of Activity in Endocrine Glands. XXIII. Emotional Polycythemia in Relation to Sympathetic and Medulliadrenal Action on the Spleen. Am. J. Physiol. 84:545-562 (Apr.) 1928.

26. Lehmann, H. E. and Hanrahan, G. E.: Chlorpromazine; New Inhibiting Agent for Psychomotor Excitement and Manic States. A. M. A. Arch. Neurol. & Psychiat. 7: 227-237 (Feb.) 1954.

27. Liddell, D. W. and Weil-Malherbe, H.: The Effects of Methedrine and Lysergic Acid Diethylamide on Mental Processes and on the Blood Adrenaline Level. J. Neurol., Neurosurg. & Psychiat. 16:7-13 (Feb.) 1953.

28. Lindemann, Erich: The Psychopathological Effect of Drugs Affecting the Vegetative System. 1. Adrenalin. Am. J. Psychiat. 14:983-1008 (Mar.) 1935.

29. Manger, W. M., Baldes, E. J., Flock, Eunice V., Bollman, J. L., Berkson, J., and Jacobs, M.: A Method for Quantitative Estimation of Epineprhine and Norepinephrine: Preliminary Report, Proc. Staff Meet. Mayo Clin. 28:526-531 (Sept. 23) 1953.

30. Manger, W. M.; Flock, E. V.; Berkson, J.; Bollman, J. L.; Roth, G. M.; Baldes, E. J., and Jacobs, M.; Chemical Quantiation of Epinephrine and Norepinephrine in Patients with Pheochromocytoma. Circulation 10:641 - 652 (Nov.) 1954.

31 Marrazzi, A. S. and Hart, E. R.: Relationship of Hallucinogens to Adrenergic Cerebral Neurohumors. Science. n.s. 121:365-367 (Mar. 11) 1955.

32. Martin, G. J.: Biological Antagonism: The Theory of Biological Relativity. New York, The Blakiston Company, 1951, p. 38.

33. Meyerhof, O. and Randall, L. O.: The Inhibitory Effects of Adrenochrome on Cell Metabolism. Arch. Biochem. 17:171-182 (Apr.) 1948.

34. Roth, G. M., Flock, E. V. and Kvale, W. F.: Pheochromocytoma: Evaluation of the Pharmacologic and Chemical Tests as an Aid to Diagnosis. Abstracts of Symposia, p. 423-431, Third World Congress of Cardiology, Brussells, Belgium, Sept. 14-21, 1958.

35. Schwarz, B. E., Bickford, R. G. and Rome, H. P., Reversibility of Induced Psychosis with Chlorpromazine. Proc. Staff Meet., Mayo Clin. 30:407-417 (Sept. 21) 1955.

36. Schwarz, B. E., Sem-Jacobsen, C. W. and Petersen, M. C.: Effects of Mescaline, LSD-2, and Adrenochrome on Depth Electrograms in Man. A. M. A. Arch. Neurol. & Psychi: 75:579-587 (June) 1956.

37. van den Heuvel-Heymans, G.: Mécanisme de l'action hyperglycémiante de l'acétylcholine, de la morphine et de la nicotine. Arch. internat. pharmacodyn. 83:386-416 (Aug. 1) 1950.

38. Vogt, M.: Communication to the British Pharmacological Society, January 5, 1952.

39. Vogt, Marthe: The Concentration of Sympathin in Different Parts of the Central Nervous System Under Normal Conditions and After the Administration of Drugs. J. Physiol. 123:451-481 (Mar.) 1954.

40. Weil-Malherbe, H.: The Effect of Convulsive Therapy on Plasma Adrenaline and Noradrenaline. J. Ment. Sc. 101: 156-162 (Jan.) 1955.

41. Weil-Malherbe, H.: The Concentration of Adrenaline in Human Plasma and Its Relation to Mental Activity. J. Ment. Sc. 101:733-755 (Oct.) 1955.

42. Weil-Malherbe, H. and Bone, A. D.: The Chemical Estimation of Adrenalin-like substanc in Blood, Biochem. J. 51-311-318 (June) 1952.

43. Weil-Malherbe, H. and Liddell, D. W.: Adrenaline and Noradrenaline in Cerebrospinal Fluid. J. Neurol., Neurosurg. & Psychiat. 17:247-249 (Nov.) 1954.

44. Woolley, D. W. and Shaw, E.: A Biochemical and Pharmacological Suggestion About Certain Mental Disorders. Science, n. s. 119:587-588 (Apr. 30) 1954.

45. Woolley, D. W. and Shaw, E. N.: Antiserotonins in Hypertension and the Antimetabolite Approach to Chemotherapy. Science, n. s. 124:34 (July 6) 1956.

DISCUSSION: Irving Pine, M. D.

The paper by Dr. Manger and his co-workers on Epinephrine and Norepinephrine in Mental Disease is an interesting and important contribution to the growing body of work and research being done on the relationship of the sympathetic adrenal system in emotional and mental disorders.

Dr. Robert McCluer of our research department, who specializes in biochemistry, has carefully gone over all the details of this paper, including chemical methods, their reactions, the statistical methods and their meanings, and also the validity of the procedures. In a personal communication to me he has assured me that the work is reliable and significant.

Dr. Manger has shown that there was no significant change in the pressor amines following administration of methacholine (Funkenstein tests). Also that in 12 patients given electroshock therapy, even though there was a transient rise of plasma epinephrine, the magnitude of pressor amine increase did not appear to be correlated with the clinical status or prognosis of these patients. Therefore, I will limit my remarks to some comments about the increase of epinephrine like substances in the plasma of healthy volunteers one-half and two hours after the administration of mescaline.

Even though the authors have commented that "the significance" of the increase in the mean concentration of epinephrine-like substance in the plasma of normal subjects, one-half and two hours after the oral administration of Mescaline is uncertain, this may still collaborate or explain why more symptoms occur with the use of Mescaline and LSD-25 in normal persons than in persons during psychosis. As the authors have shown, the fact that no increase in the mean concentration of epinephrine-like substance occurred in four patients with mental disease after administration of Mescaline suggests that a difference may exist between physiochemical responsiveness of some psychiatric patients and of normal subjects. However, this also may suggest that after a period of time the patient's behavior and disorder in psychosis is such that there occurs a fatigue process or depression of the sympathetic adrenal system. In any event these findings may not necessarily be the cause of, contributory to, or even indicating a responsiveness towards, but perhaps an end result of the body's reaction to psychotic disorder, whereas in the so-called normal person, as demonstrated in this paper, there is an increase in the concentration of epinephrine-like substances in the plasma of the subjects tested.

Regan & Reilly studied "Circulating Epinephrine & Norepinephrine in Changing Emotional States" in 60 hospitalized psychiatric patients and found that the levels tend to change with changes in an individual's emotional state. Thus the catecholamines may distinguish certain subgroupings of patients or individual change but could not be correlated according to the usual psychiatric classification.

Since the effect of LSD on the epinephrine-like substances in the plasma was not the same as Mescaline in normal subjects, some important questions are raised about the differences and their site of action; and also one wonders about the fact that there were only four psychotic patients who, in this instance, could be classified perhaps as controls since their levels of epinephrine-like substances remained the same.

This paper opens up wide avenues of research and also raises many other stimulating questions. The ones that occurred to me are, 1) what would have been the value of doing simultaneous studies with serotinin? 2) what would have been the value of studying the effect of these substances while the normals and psychotics were under the influence of large doses of tranquilizing drugs; and finally, 3) what is the meaning of this type of approach as has been mentioned by Brodie where, in order to gain knowledge about mental illness, we find that we have to study more changes perhaps at least from the biochemical point of view in the normal subject.

I think that Dr. Manger is to be congratulated for this most interesting and stimulating paper.