BIOLOGICAL INDICATORS IN PSYCHIATRY

by

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The psychiatric diseases that can be diagnosed by completely objective methods can almost all be counted on the fingers of one hand. They are: general paresis of the insane, i.e. syphilitic meningo-encephalitis, pellagra, porphyria and a few rare inborn errors of metabolism, for instance, phenylketonuria, which is associated with a specific type of mental deficiency. Two other types of mental deficiency that are also diagnosable by objective methods are cretinism and Down's syndrome or mongolism.

Fagge at Guy's Hospital in London postulated in 1871 that the absence of the thyroid gland was the cause of myxedema and cretinism. Then, in 1909, Wassermann developed his serological test of syphilis, and for the first time made it possible to diagnose general paresis unequivocally. Soon afterwards Noguchi demonstrated spirochetes in the brains of patients who had died from general paresis, and the breakthrough of psychiatry to the rest of medicine seemed to have occurred. However, the model of general paresis remained an isolated example, and diagnostic laboratory methods for most of the psychiatric diseases today, as well as their etiologies, are still unknown.

In 1934 Folling discovered that a particular type of mental deficiency, representing, however, only 0.7 per cent of all mentally retarded, was caused by an inborn deficiency of phenylalanine hydroxylase and could be diagnosed by a grossly elevated level of plasma phenylalanine or by the presence of phenylpyruvic acid in the urine. I still remember the excitement when, in the early forties, we screened all our mentally retarded at the hospital and diagnosed our first case of phenylketonuria as the urine turned green on the addition of ferric chloride. A simple urine test for a psychiatric disorder!

In 1937, Elvehjem discovered that the black tongue syndrome in dogs and pellagra in man were caused by a diet deficient in nicotinic acid and could be diagnosed by measuring its metabolites, i.e. N-methylnicotinamide and pyridone, in the urine.

In 1959, Lejeune, Gautier and Turpin showed that patients with Down's syndrome, a much more common type of mental deficiency than phenylketonuria, had 47 instead of 46 chromosomes, with trisomy of chromosome 21 (Fig. 1). Another objective diagnosis! But that is all there is for psychiatry. General paresis and pellagra had all but disappeared since

their causes and a treatment for them were discovered. At any rate, they have become diseases of general medicine rather than psychiatry. Phenylketonuria and Down's syndrome are still with us, while cretinism is hardly seen any more, but these are types of mental deficiencies rather than psychiatric diseases.

The fact is that, apart from porphyria and some mental disorders caused by toxic agents or by gross structural changes in the brain, e.g. tumors, when biochemical tests, X-rays, electroencephalograms and neurological examinations can sometimes determine the diagnosis, psychiatric diagnoses - in probably 90 percent of cases - are made on the basis of behavioural observations. Certainly, the major functional psychoses, e.g. schizophrenia and paranoid states, the affective disorders and all neurotic illnesses - but also most organic psychoses - are today diagnosed almost exclusively on the basis of behavioural symptoms in the areas of cognitive, perceptual, affective and interpersonal functioning.

Man's organism, is, of course, subject to biochemical and physiological laws, and that includes his behaviour and private experiences. But human behaviour and experiences are so complex, the resultants of so

many different factors, that until now we have not been very successful in reducing these psychological functions to biological parameters, both representative and simple enough to be expressed in pointer readings of laboratory instruments.

Consequently, psychopathology has developed until quite recently along lines of theoretical constructions based on psychodynamic concepts of psychoanalysis or behavioural concepts of learning theory. That has not always been to the benefit of psychiatry, but it is only during the last two decades that some beginnings have been made to study and measure the biological substrates of psychopathology. This research is still inadequate, entirely experimental, and often highly speculative, but it is promising enough to give us hope that in the next decade at least some biological indicators of clinical interest to the practicing psychiatrist will be developed.

We know today that ability and inability to cope have their chemical counterparts. We have learned a great deal about the anatomy and physiology of primitive drives like hunger, thirst and sexuality, but also about the physiological aspects of social play and different forms of aggression.

We can study the chemical correlates of reward and punishment, of sleep, dreams, arousal, even of simple forms of memory. All this must eventually pay off in some improved technology of diagnosis in clinical psychiatry.

Three times in the history of psychiatry its hopes for a breakthrough to biology have been sadly dashed. The first time, early in our century, when the diagnosis of general paresis turned out to be an isolated incident rather than the beginning of a general development and a new era; the second time when Berger's discovery of the electroencephalogram in the late twenties became an invaluable diagnostic tool for neurologists but did not provide the royal road to psychiatric diagnosis as many had assumed; the third time, in the early thirties, when the discovery of the Norwegian psychiatrist Gjessing, that a rare form of schizophrenia, i.e. periodic catatonia, was regularly associated with measurable changes in the patient's nitrogen balance (Fig. 2), failed to usher in a host of similar new discoveries, as many had expected.

We badly need biological indicators for the diagnostic process in psychiatry in order to free it as much as possible from the subjectivity which still prevails in this field and, more specifically, to make objective

measurements possible for the purposes of:

1. making a nosological diagnosis;

2. monitoring changes of the disease process, e.g. improvement or worsening;

3. establishing homogeneous groups in patients with identical symptoms, e.g. among various depressed patients;

4. predicting therapeutic effectiveness of different procedures and agents, e.g. psychotropic drugs;

5. obtaining heuristic relationships between behavioural and biological variables to explain central mechanisms of action.

Three different methodologies are available to furnish those indicators. The first methodology is concerned with psychophysiological indicators, i.e. the measurement of autonomic functions that reflect psychological processes. The polygraph has in the last three or four decades become the standard instrument for the measurement of autonomic responses, for instance skin conductance, vasodilatation, muscle tension, blood pressure and heart rate. The so-called lie-detectors are polygraphs that measure autonomic responses associated with emotional arousal and tension, not necessarily lies.

Fig. 3 shows one way in which skin conductance measurements can be used to monitor changes in a patient's stress tolerance - in this case during a depressive episode - before and after electroconvulsive treatment. The patient's skin conductance is lower, i.e. he is less aroused autonomically, after the treatment, and this lowering of arousal is most marked during a stress interview period. Fig. 4 displays the plethysmographic measurement of the increased forearm blood flow of a patient suffering from chronic anxiety as compared to a normal control. Table I gives the different values for forearm blood flow in different psychiatric disorders. Note that the mean values for personality disorder, non-agitated depression and phobic, i.e. specifically focussed anxiety, are below the control measures; but another form of neurosis, namely chronic, diffuse anxiety gives maximal measures. The investigator reporting these results also found that the very high values of forearm blood flow in chronic anxiety could serve as a predictor of therapeutic success with psychosurgery.

Changes in voice characteristics, as exhibited in a sound spectrogram, have been shown to be correlated with academic performance of students (Gilmore and Willis, 1970). In relation to learning efficiency,

heart rate was found to discriminate better than skin conductance, muscular tension, respiration rate and finger temperature between people with high and low anxiety levels (Wilson and Wilson, 1970). Schizophrenic patients were shown to have higher amplitudes, shorter latencies and faster recovery times of skin conductance than controls, and the investigators reporting these findings speculate that this is mediated via frontal-limbic pathways and that schizophrenic behaviour is the result of temporal and limbic lobe dysfunction (Gruzelier and Venables, 1972). Another group of workers observed a tendency toward lower skin conductance in depressed patients and interpret this as an indication of hypothalamic dysfunction in these patients (Noble and Lader, 1971).

The second methodology that potentially can provide biological indicators that reflect psychiatric disorders is based on neurophysiology. This discipline is a relative newcomer to the behavioural sciences and could begin to contribute clinical data in humans only after electroencephalographic techniques had been developed. The EEG allows us to go beyond the peripheral autonomic responses which are measured by the polygraph and to study directly some spontaneous and responsive activities

of the human central nervous system. In recent years the techniques and methodologies of the EEG have been greatly refined, and more sophisticated developments have focussed interest on the study of average evoked potentials and the so-called event-related slow potentials, e.g. the contingent negative variation.

Fig. 5 shows the EEG record of a man with psychomotor epilepsy which manifested itself mainly in psychiatric symptoms. Note the distinct left anterior temporal spikes. Unfortunately, in most similar cases it is very difficult or impossible to obtain such clear diagnostic evidence. Fig. 6 and 6a demonstrates the neurophysiological changes that have taken place over a period of two years in a woman, aged 72, who is suffering from senile dementia. The second EEG is characterized by considerable slowing of cerebral electrical activity; such increased slowing is regularly associated with increasing dementia. Here we are dealing with an organic psychosis, at the borderline between neurology and psychiatry, where biological indicators, like the EEG, assume much greater importance than in the realm of functional psychiatric disorders.

Fig. 7 gives an example of an objective criterion for the screening

out of homogeneous groups in a population of depressed patients, i.e. bipolar (with manic and depressive episodes) and unipolar (with recurrent depressions only) depressives. The two groups are here differentiated on the basis of the amplitude of one particular component of an average evoked response. These results have, to my knowledge, not been confirmed. Also, they are merely empirical observations and a far cry from such differentiations in other branches of medicine, for instance, of two different types of hyperglycemia of which one is associated with increased insulin secretion and the other not (Fig. 8).

Fig. 9 shows the different evoked potential recovery curves for schizophrenics and normals; note the greater and faster recovery of the controls. Fig. 10 gives evoked response patterns of a chronic schizophrenic and a normal volunteer. This particular schizophrenic exhibits shorter latencies, lower amplitudes and higher individual variability. But it has also been reported that the resting EEG of schizophrenics is characterized by lower than normal variability - a remarkable finding, since almost all other physiological measures in schizophrenics are more variable than the norm (Goldstein et al., 1965).

The third methodology that can serve as a source of biological indicators in psychiatry is biochemistry. The rapid advances of biochemical and neuroendocrinological methods that have taken place during the last twenty years have produced many new insights into the pathophysiology of psychiatric disorders. They have also given rise to several theories about the etiology and have opened up new possibilities for the measurement of behaviour-linked metabolic variables. New hypotheses and new techniques in this latest field of biopsychological measures are being developed at an unprecedented rate, as the study of cerebral metabolism, and especially the effects of biogenic amine neurotransmitters, has moved into the spotlight of active laboratory research.

One research approach to schizophrenia has for many years focussed on discovering a toxic factor in the plasma of schizophrenic patients. Table II gives an impression of the extension and the uncertainty in this field. Seventeen different investigators had reported by 1967 on various factors they thought they had isolated in the plasma of schizophrenics. Seven had found that their factor was contained in the alpha globulin fraction, three that it was a beta and one that it was a gamma globulin.

Twelve investigators did not identify their schizophrenia factor.

Fig. 11, a histogram taken from a more recent paper (Amkraut et al., 1973), shows that serum immunoglobulin levels are elevated - specifically IgG, IgA and IgM - when compared to controls. However, it is also quite obvious that there is considerable overlapping of patient and control measures, which makes this finding more interesting to the statistician and the hypothesis-seeking researcher than to the practicing psychiatrist.

Fig. 12 displays immunoelectrophoretic patterns of antibrain globulin in schizophrenics as distinguished from inactive preparations in healthy controls. This figure is taken from a paper by Heath who has separated an antibody fraction that he called Taraxein from the blood of acute schizophrenics. Heath claims that this fraction is contained in gamma globulin and possesses the properties of causing characteristic changes in the EEG recorded from electrodes implanted in rhesus monkeys as well as producing transient psychotic states in normal volunteers who were injected with Taraxein. This research is almost 20 years old but has not yet been confirmed.

Fig. 13 demonstrates the presence of Frohman's factor, a beta

globulin which is found in the blood of schizophrenics and increases the lactate/pyruvate ratio in chicken erythrocytes. Again, the presence of this factor has not been satisfactorily confirmed.

Fig. 14 refers to temporary increases in indole metabolites in the urine of schizophrenics during periods of acute psychotic disturbance. Fig. 15 shows the urinary excretion of tryptamine and total indole-3-acetic acid as related to the degree of psychotic activity.

Fig. 16 evokes memories of the times - not so long ago - when the best we could do to register changes in the levels of glucocorticoids was to count eosinophils in the patient's blood. In 1952 Dr. Mann and I undertook a little investigation in order to determine to what extent the then newly discovered glucocorticoids played a part in depressive conditions. The low eosinophil counts reflect increased adrenocortical activity and are regularly associated with depressive episodes. This is not surprising since glucocorticoids are stress hormones, and depression is a major stress. During a remission adrenal corticoid levels are lower, and the eosinophil count rises. One interesting observation we made is reflected in the eosinophil-corticoid reactions between days 45 and 54

on this graph. During this period the patient was relapsing into depression, her eosinophil count decreasing. But then she suddenly began to express paranoid ideas of persecution - in psychiatric lingo one would say the patient no longer turned aggression against herself but projected it onto others. This psychodynamic defence-maneuver had the effect of relieving her stress and consequently led to a temporary rise of eosinophils. A week later she became typically depressed, no longer paranoid, and at that point her eosinophils plunged to the bottom. Perhaps our analysis is pushed too far, but if it is correct this would be one of the rare examples where the stress values of different psychodynamic defences have been transduced into biological parameters.

Fig. 17 is taken from an important paper by Pollin et al. (1972) in which the authors examined homozygotic twins who were discordant with regard to schizophrenia, i.e. one of the twins was psychotic, the other not. The graph shows that normal controls and the healthy twins are in the same category as far as corticoid metabolites are concerned - the healthy twin excretes normal amounts of 17-OH, the psychotic twin increased amounts - but when it comes to catecholamines and their metabolites -

epinephrine, norepinephrine and dopamine - both twins excrete higher than normal amounts. This study demonstrates fairly convincingly that the corticoid hormones seem to be determined by the patient's phenotype - or his stress level - while the catecholamines in schizophrenia appear to serve as a genetic marker and are determined by the patient's genotype.

Fig. 18 reviews results of plasma cortisol determinations in depressed patients obtained by eight investigators. All of them found significantly higher cortisol levels in depressed patients than in normal controls, an unspecific result one would expect in view of the extreme stress situation in which every depressed individual finds himself.

Fig. 19 represents an interesting attempt to use the increased plasma corticoid levels in depressed patients as warning indicators of impending suicide. The patient who consistently had the highest corticoid levels finally committed suicide; another depressed patient commenced to have suicidal thoughts when his intolerable depressive stress was reflected in a sudden rise of plasma corticoids. Interesting as these

observations are, they can not yet replace clinical vigilance at the behavioural level.

Table III gives the mean norepinephrine, 5-HT and 5-hydroxyindoleacetic acid levels in the hindbrains of people who committed suicide, other depressives and coronary controls. You note that the level of the serotonin metabolite 5-hydroxyindoleacetic acid is significantly lower than that of the controls in the suicides and the other depressives. This is in accordance with the hypothesis of the "indoleamine school" which maintains that depressions are associated with a diminished serotonin level in the brain.

Similarly, Table IV shows that the mean value of tryptophan concentration in the spinal fluid of depressed patients is significantly lower than that of controls. One should mention here that it is now known that much of the indoleamine concentration in the CSF - as well as that of their precursors and metabolites - may come not from the brain but from the spinal cord. Also note that there is again considerable overlapping in that individually several of the depressed patients have higher tryptophan values than the controls.

Coppen et al. (1973) found that the acid-soluble plasma level of free tryptophan in depressed women was significantly reduced. It increased when the patients recovered but did not attain normal levels, thus suggesting that the lower plasma level of free tryptophan may be a constitutional marker of vulnerability to depressive breakdowns.

Fig. 20 is in support of the "catecholamine school" of depression which claims that a relative deficiency of catecholamines, as well as their precursors and metabolites, characterizes the depressed state. Benkert et al. (1971) could demonstrate that the plasma level of tyrosine - the precursor of dopa - was significantly lower in endogenously depressed patients than in neurotic depressives, schizophrenics and healthy controls when measured at 11:00 a.m.

Fig. 21 shows how the urinary excretion of normetanephrine increases in a depressed patient about 10 days after treatment with the antidepressant drug imipramine has been started. At the same time the lowering of the score on a depression rating scale indicates chemical improvement.

Fig. 22, also in support of the "catecholamine school" of affective disorders displays an impressive increase of urinary epinephrine one day prior to the sudden onset of an episode of manic behaviour.

Schildkraut et al. (1973) suggest that the urinary level of 3-methoxy-4-hydroxyphenylglycol (MHPG) may serve as a biological basis for classifying depressive disorders and predicting responses to specific forms of pharmacotherapy. They found a general tendency for MHPG to be reduced in the urine of depressed patients, but more so in bipolar than in unipolar depressions, and more in the latter than in chronic depressive characterological disorders.

Sjostrom and Roos (1972) determined spinal fluid concentrations of 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) in groups of manic, depressed, other psychiatric patients and controls. Manic patients had higher concentrations of HVA than the other three groups. After loading with probenecid, the increase of 5HIAA and of HVA in the manic and depressed patients was significantly smaller than in the other two groups. These findings suggest decreased turnover rates of dopamine and 5-hydroxytryptamine in the two phases of manic-depressive psychosis.

In 1963 Friedhoff and Von Winkle reported the discovery of a substance in the urine of schizophrenic patients that could be detected as

a pink spot on the chromatogram and that they identified as 3,4-dimethoxy-phenylethylamine (DMPEA). They proposed that DMPEA was a toxic substance that caused the behavioural abnormalities of schizophrenics. However, after twelve years the question whether the "pink spot" is really specific for schizophrenia or not is not yet settled. The spot is often absent in chronic schizophrenics, and its appearance seems to be related to dietary factors. Even its identification as DMPEA has been questioned (Friedhoff and Von Winkle, 1963; Faurbye and Pind, 1964, Stabenau et al. 1970).

Finally, Fig. 23 reflects some intriguing recent research by Meltzer (1974). This investigator has pursued for several years his work on increased activity of creatine phosphokinase and aldolase in the serum of most patients during acute phases of functional psychoses, apparently due to an increased efflux of these enzymes from skeletal muscle. In 16 of 24 psychiatric patients he found abnormal muscle biopsies. This figure shows camera lucida drawings of muscle biopsies of two paranoid patients. Section A shows the distribution of one motor nerve axon to five different muscle fibers. In normal controls

fewer than 10 per cent of the nerves innervate more than one muscle fiber. In section B several immature sprouts of one nerve terminate in only two or three recognizable nerve endings.

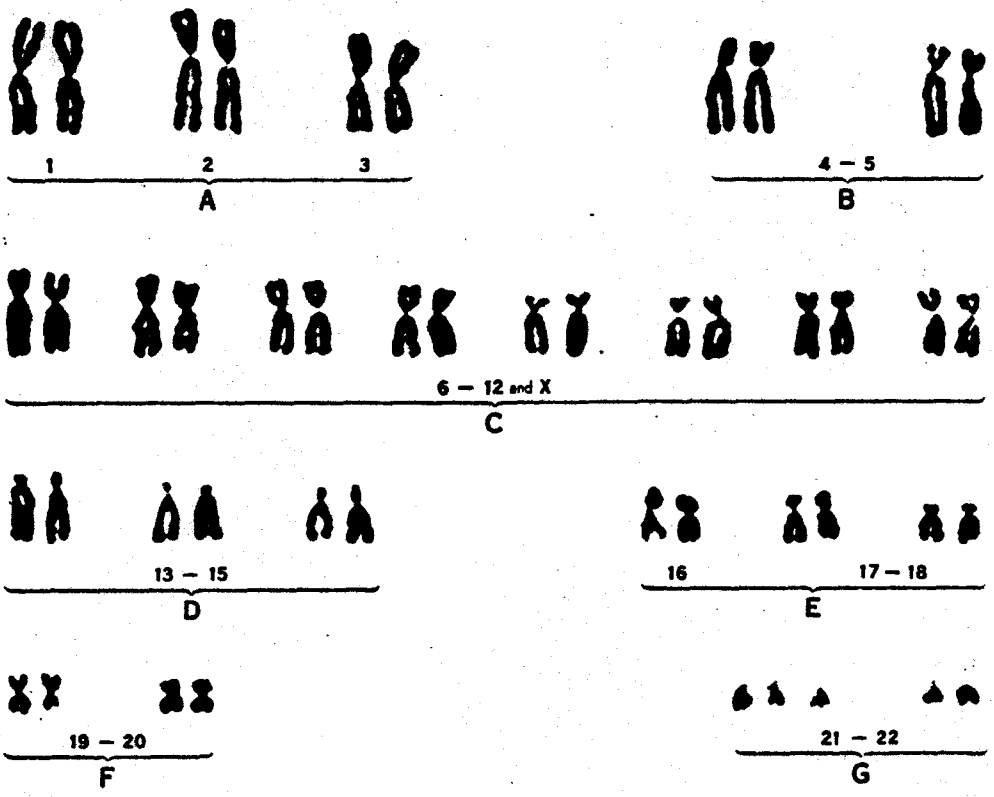
Meltzer claims that his findings are so far the strongest evidence for neuropathological changes in the functional psychoses, and he feels that, if his findings can be confirmed by others, the term "functional" for these psychoses may be dropped, since organic changes in the nervous system of patients suffering from these psychoses have been demonstrated.

This strikes me as an unduly optimistic prediction at the present time. Increased creatine phosphokinase levels in the serum may accompany many acute psychotic episodes. However, such findings are neither consistently present nor sufficiently specific. Moreover, there is at the present time no theory that could explain the empirical findings of abnormal muscle biopsies in patients suffering from mental disorders.

On the other hand, there are now well developed theories connecting the biogenic amine neurotransmitters with affective disorders. But the reliability of the various biochemical indicators that have been proposed for the assessment of affective disorders in various body fluids is not

yet good enough to be safely applied and interpreted by the clinicians.

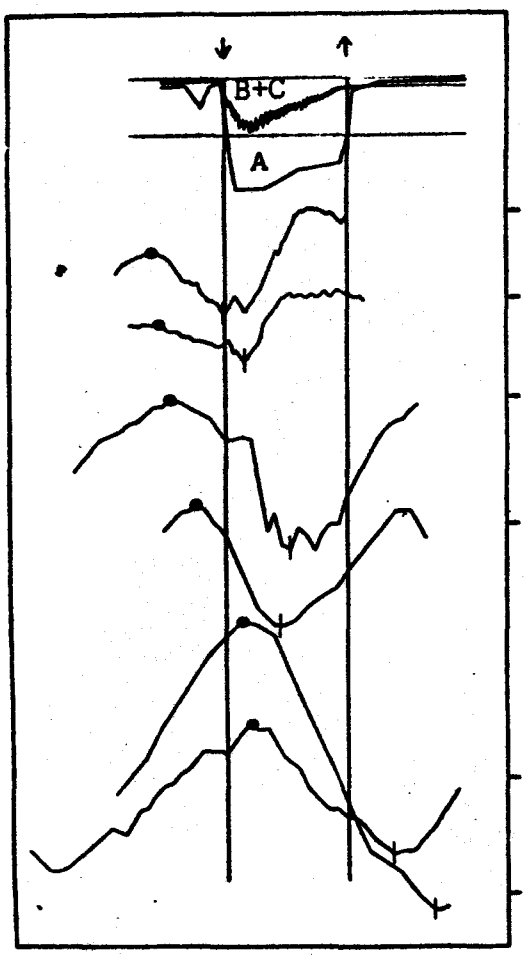
The psychophysiological and neurophysiological indicators that are available today for the psychiatrist may often be helpful in the complete assessment of a psychiatric patient but do not allow him to base his diagnosis or important clinical decisions mainly on these data. A great deal of dynamic work is going on in this area of biological indication of psychiatric disturbance, and the prospects for the near future are promising. But at this time the most reliable instrument for the assessment of psychiatric disease is still a well trained and experienced psychiatrist.



The chromosomes in mongolism. The chromosomal constitution is that of a normal female except for the presence of an extra chromosome in the set numbered 21.

McKusick, 1970

Fig. 1



ABILITY OF CONCENTRATION

EXCITEMENT

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STUPOR

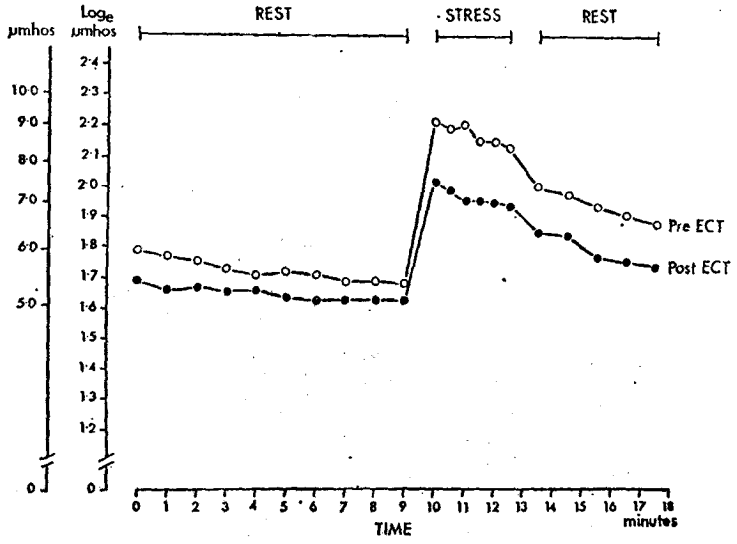
"

Maxima and minima in nitrogen balance related to the psychotic phase.

Gjessing , 1974

Fig. 2

Skin conductance



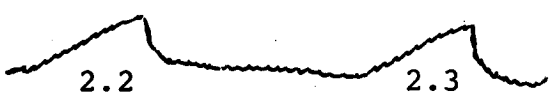
. Mean skin conductance levels: pre- and post-ECT.

The means for the skin conductance data are illustrated above. Throughout the recording skin conductance was slightly lower subsequent to ECT but the difference is not statistically significant. The stress of mental arithmetic was associated with a sharp increase in skin conductance which then fell slowly towards the basal level. The difference between the basal and stress recordings (reactivity) was highly significant (pre-ECT: $t = 6{\cdot}3$, $P < 0{\cdot}001$; post-ECT: $t = 5{\cdot}3$, $P < 0{\cdot}001$). Reactivity was reduced subsequent to ECT ($F_{1,30} = 4{\cdot}19$, $P = 0{\cdot}05$).

Noble and Lader, 1971

Fig. 3

Anxiety state



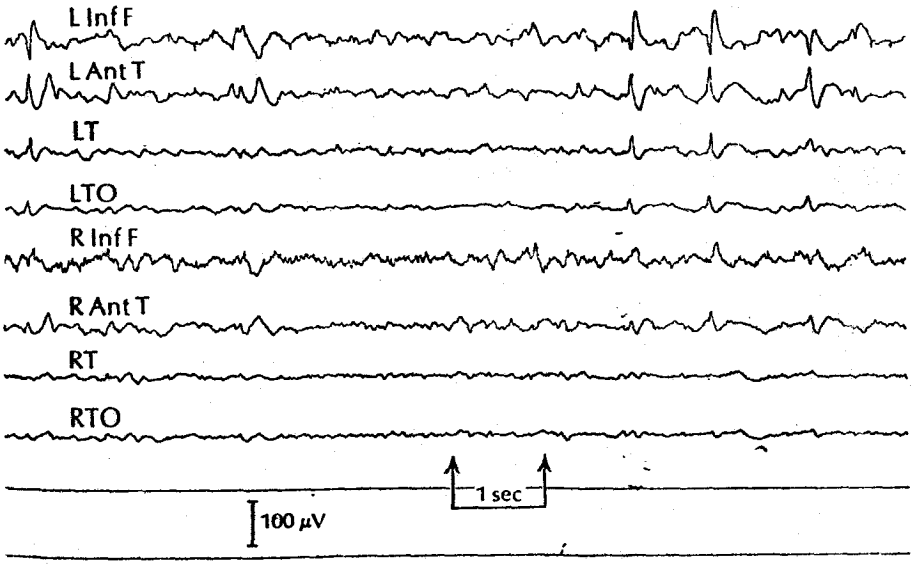
Normal control

The forearm blood flow, recorded at 30 sec intervals during a resting period, from a normal control and a patient with chronic anxiety.

Kelly, 1971

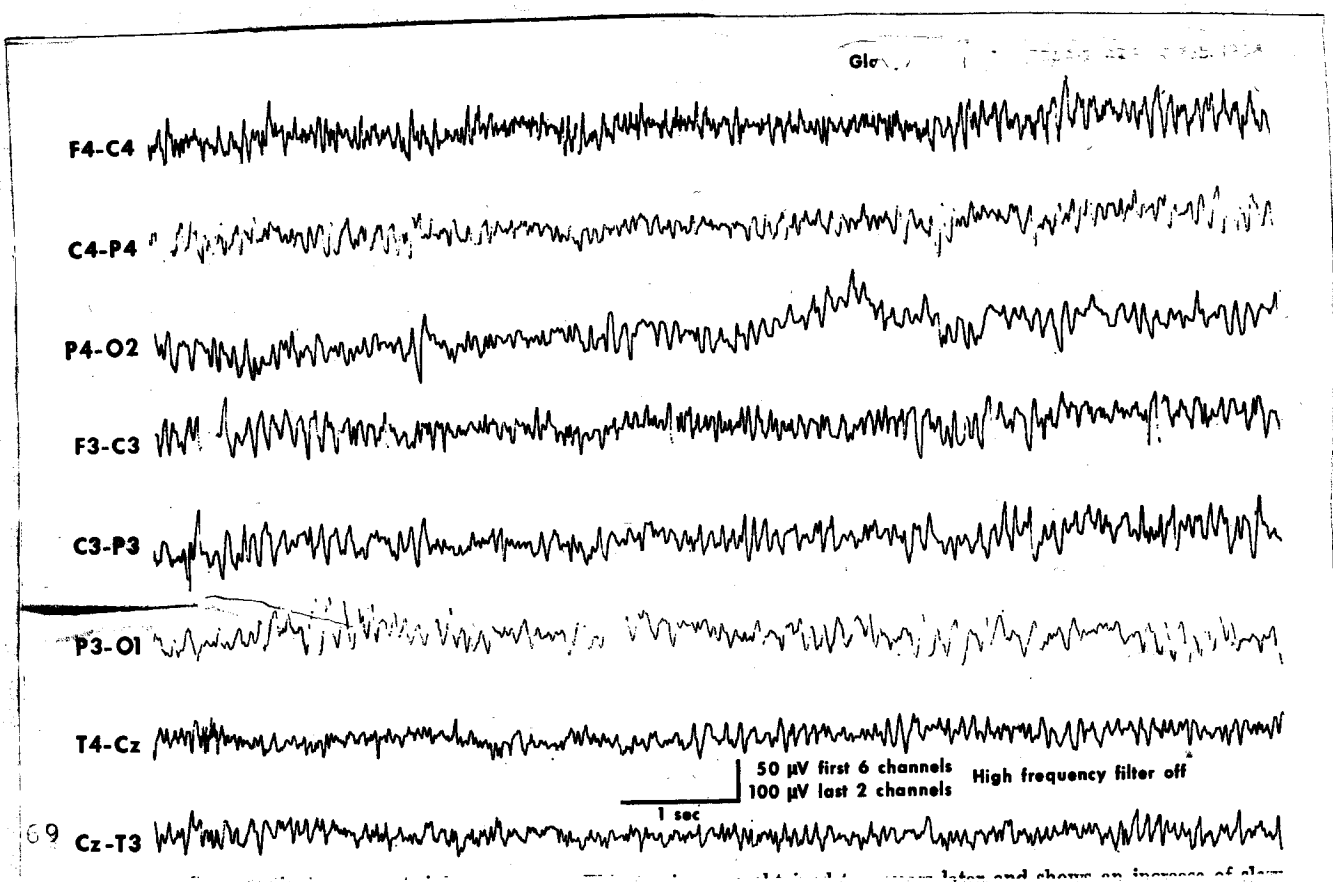
Fig. 4

EEG record of a forty-six-year-old man with psychomotor seizures. There are well-localized left anterior temporal spikes. L Ant T left anterior temporal.



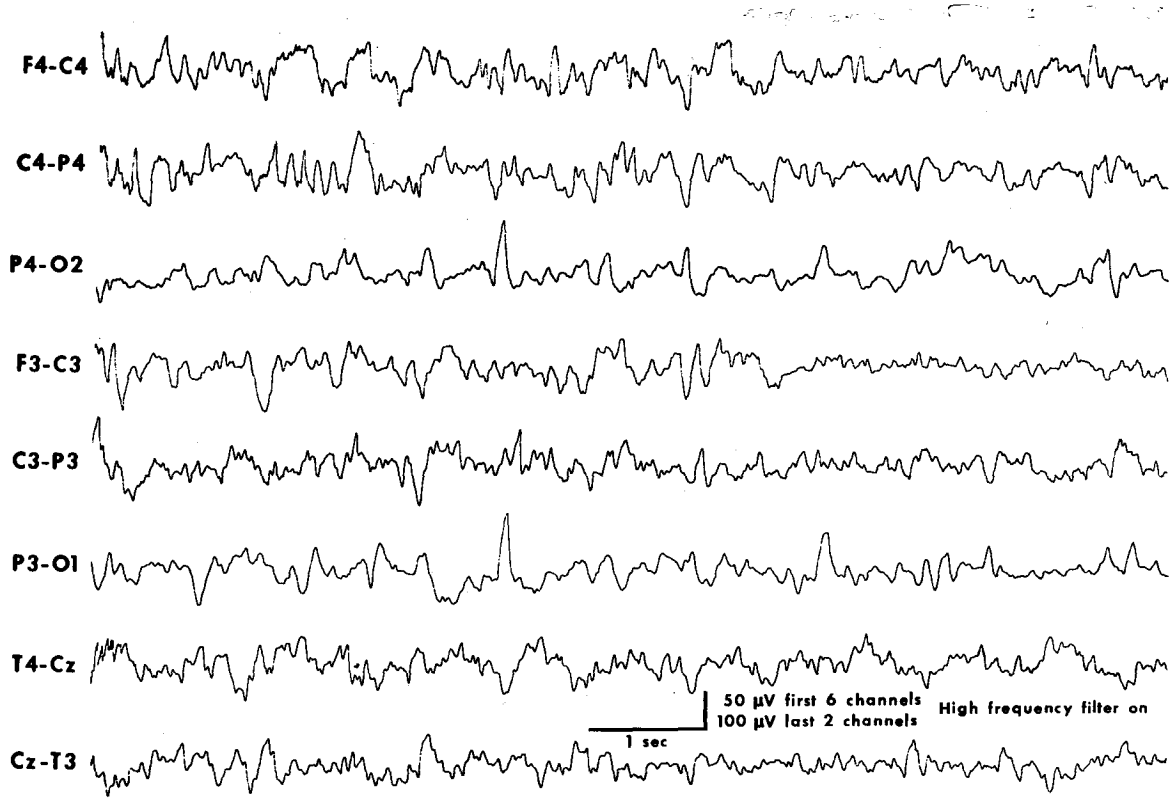
Pincus and Tucker, 1974

Fig. 5



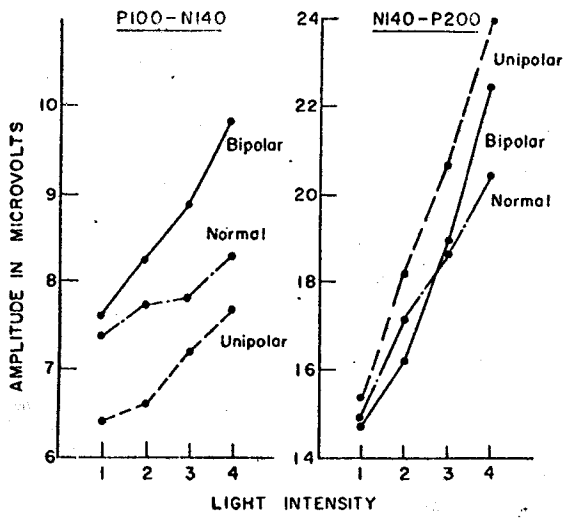
Müller, 1969

Fig. 6



Müller, 1969

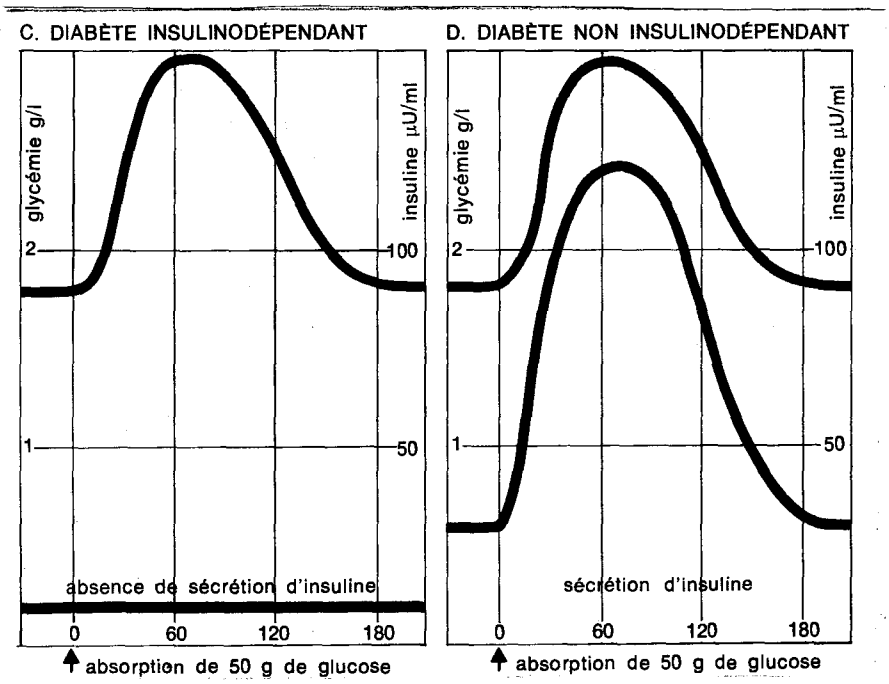
Fig. 6a



Mean average evoked response amplitude for components P100-N140 and N140-P200 for bipolar, unipolar and normal groups.

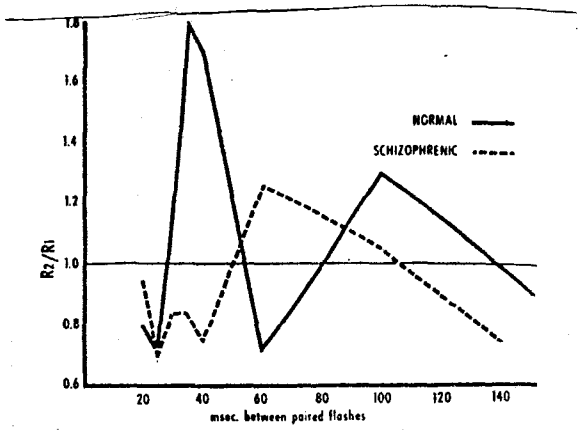
Buchsbaum et al, 1973

Fig. 7



Lestradet, 1974

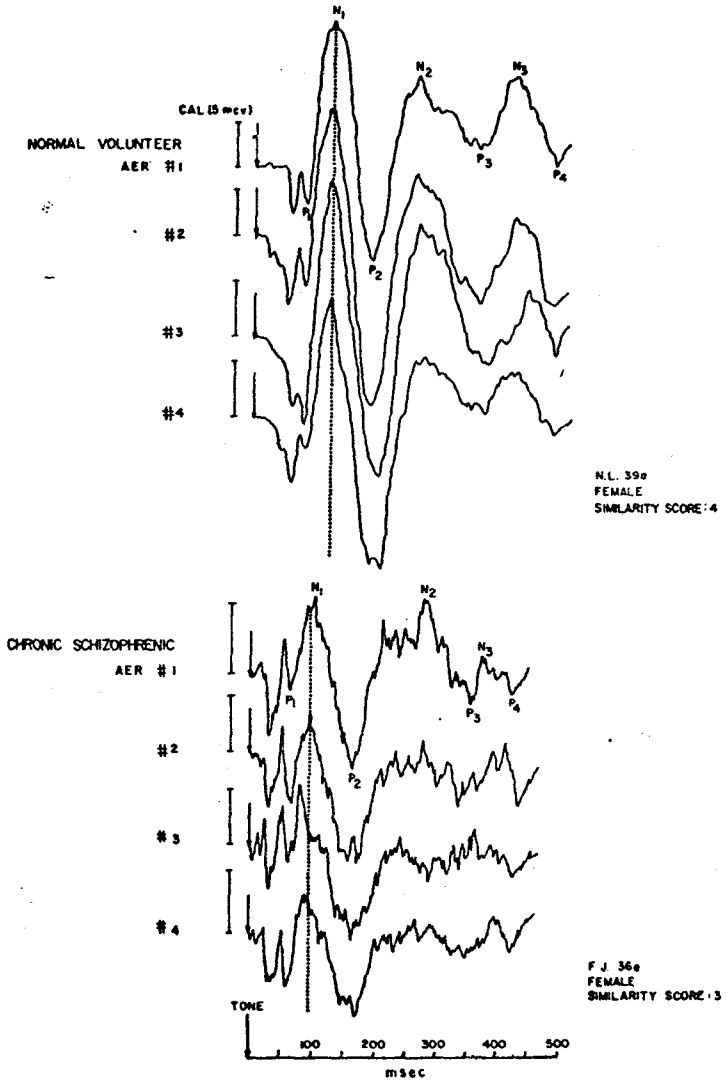
Fig. 8



--Human visual evoked response recovery function curve for deflection O_{III}.

Speck et al, 1966

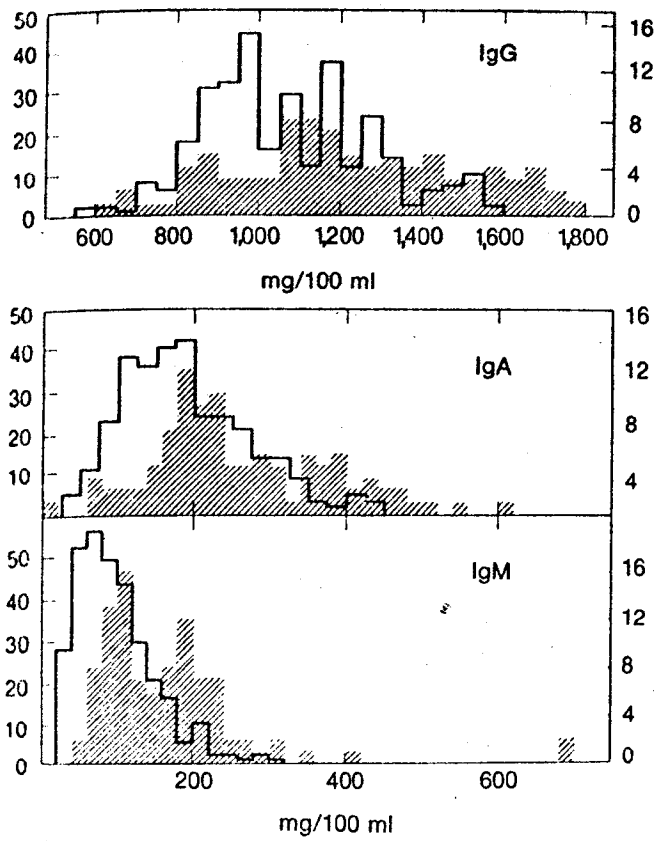
Fig. 9



Auditory evoked response of a normal volunteer and a chronic schizophrenic patient. Four AEPs of a normal volunteer and a chronic schizophrenic patient are shown in the figure. The latter exhibits shorter latencies, smaller amplitudes and a higher intraindividual variability.

Saletu et al, 1973

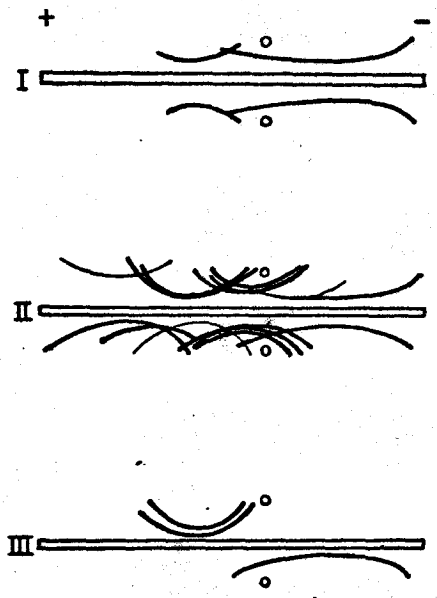
Fig.10



Serum immunoglobulin levels. Shaded area indicates number of patients; delineated area, number of controls.

Amkraut et al, 1973

Fig.11

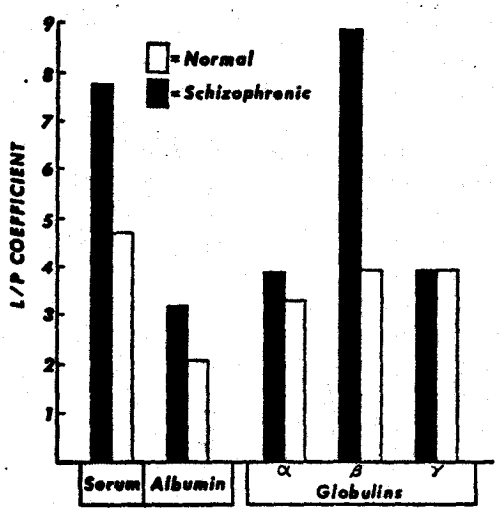


Immunoelectrophoretic patterns of human serum globulins separated by various technics. Antihuman serum used in the troughs. I, 33% saturated ammonium sulfate method. Top well: globulin fraction from acute schizophrenic patient, active preparation. Bottom well: globulin fraction from healthy control subject, inactive preparation. II, 50% saturated ammonium sulfate method. Globulin fractions from chronic schizophrenic patient. Top well: active preparation. Bottom well: inactive preparation. III, sephadex column fractionation methods. Globulin fractions from acute schizophrenic patient. Top well: Sephadex G-200 preparations of residual supernatant after some globulins were removed by 33% ammonium sulfate method; α-2-globulins are conspicuous, inactive preparation. Bottom well: DEAE Sephadex separation of α-G from whole serum, active preparation.

Heath, 1970

Heath, 1970

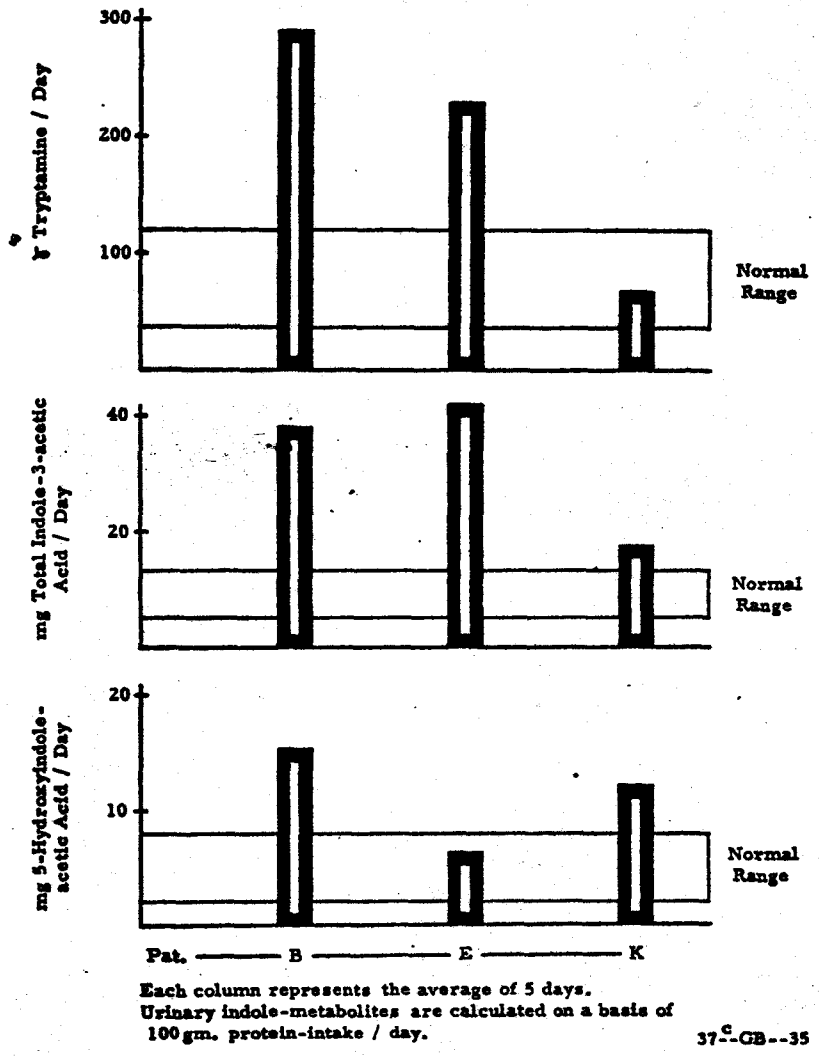
Fig. 12



The activity of different protein fractions of the blood serum of schizophrenic patients as shown by the lactate/pyruvate (L/P) ratio. The fractionization of the globulins was accomplished by electrophoresis.

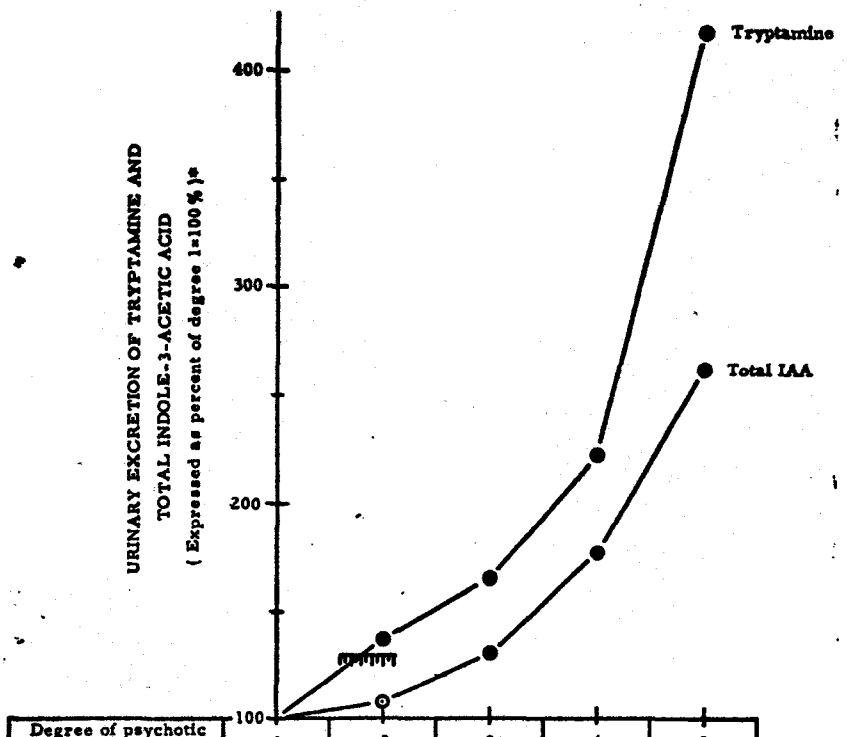
Snezhnevsky and Vartanyan,1970

Fig.13



Urinary excretion patterns of three indole metabolites during exacerbations of the psychosis in three schizophrenic patients. Each column represents the average value for 5 days. Urinary indole metabolites are calculated on a basis of 100 g protein intake per day. Himwich, 1970

Fig. 14



Degree of psychotic activity	1	2	3	4	5
Days of investigation	410	270	105	40	10
No. of patients	17	12	7	6	2

* The values are calculated on a basis of 100gm. protein-intake / day.

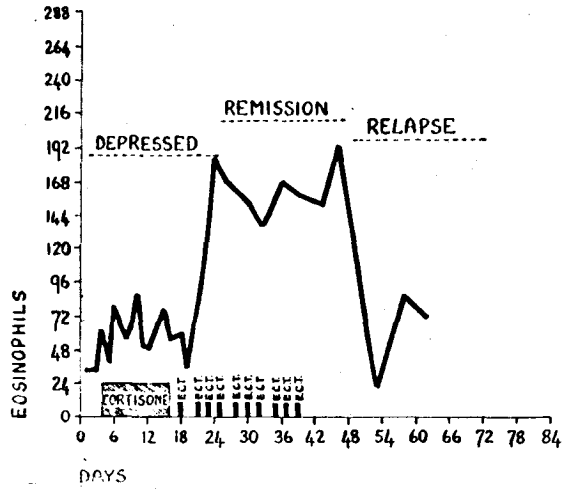
▒▒▒▒ = Upper limit of normal range.
(Total IAA = 100 % is slightly above the upper limit of normal range)

●=P<0.01
⊖=P>0.01 = Probability of difference from degree 1.

37-C-GB--33

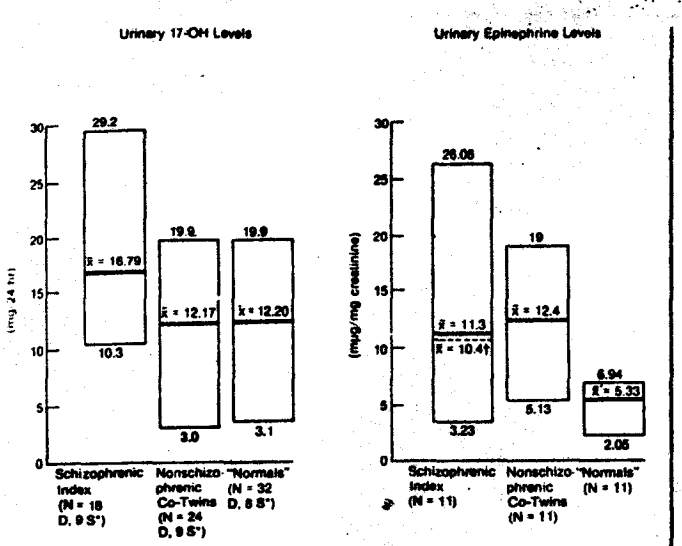
Urinary tryptamine and total 3-indoleacetic acid as related to the degree of psychotic activity. The increases for urinary tryptamine and total 3-IAA, plotted in the ordinates, are expressed as percent of the values of 100 g/day protein intake. The abscissas represent, in turn, the degrees of psychotic activity, the number of days of investigation, and the number of patients observed in each degree of psychotic activity. The circles denote the average excretions for these indole substances; black circles indicate significant differences and the one open circle is for a difference which is not significant. Himwich, 1970

Fig. 15



-Eosinophil response to therapy during a depressed episode. Remission followed by relapse.
Mann and Lehmann. 1952

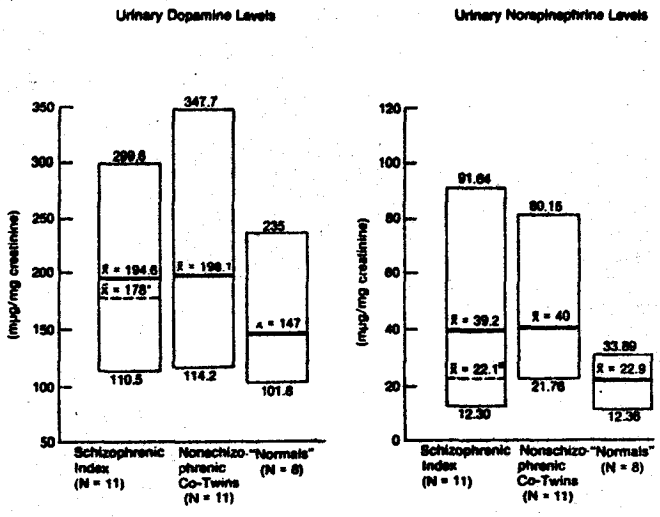
Fig. 16



Urinary 17-OH and urinary epinephrine levels.

* *D* indicates number of determinations and *S*, number of subjects.

†---indicates cc pair group means.

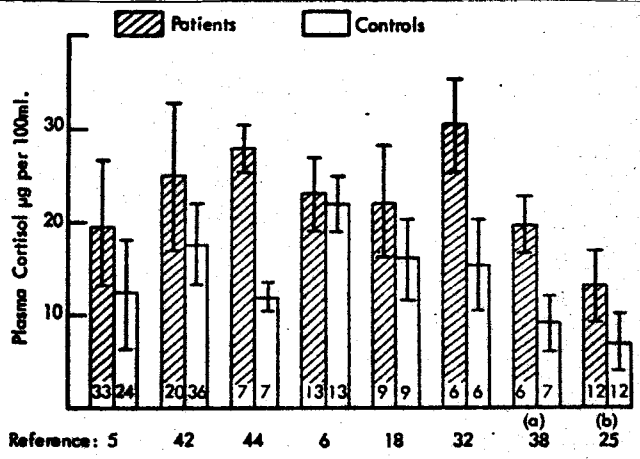


---Urinary dopamine and urinary norepinephrine levels.

*----indicates concordant pair group means.

Pollin, 1972

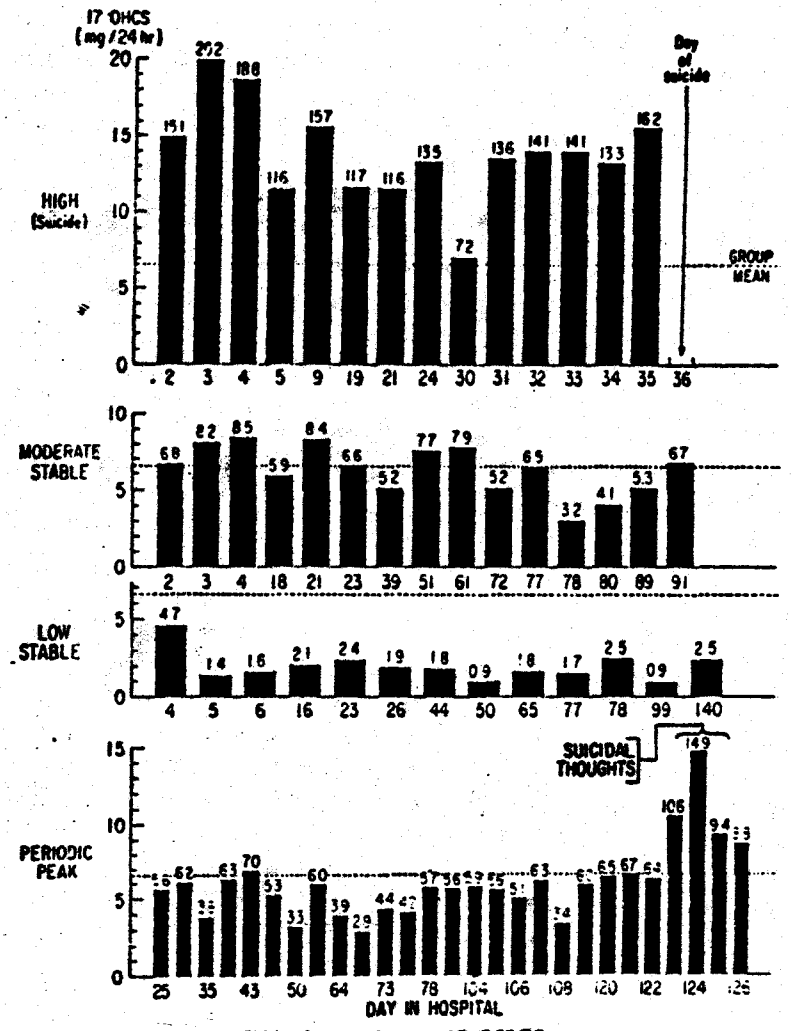
Fig. 17



Mean plasma cortisol levels (±1 S.D.) in groups of depressed patients and controls reported in the literature. The digits at the base of each column indicate the number of subjects studied. All estimations were performed at 8 to 9 A.M. except (a) 4 A.M. and (b) 2 P.M.

Gibbons, 1970

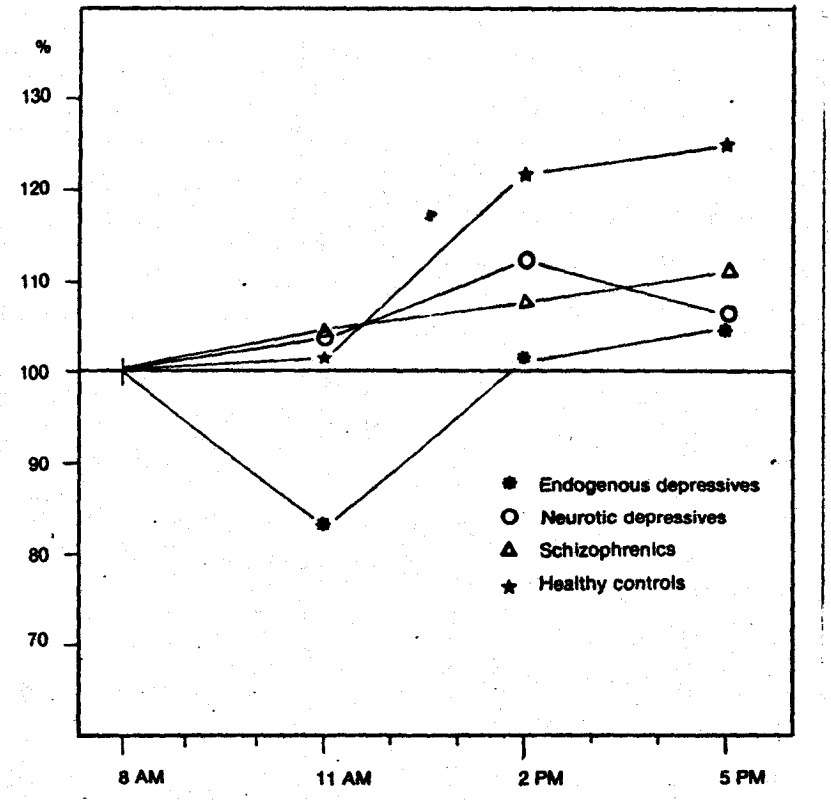
Fig. 18



Differing urinary 17-OHCS response patterns in four depressed patients.

Bunney and Fawcett, 1965

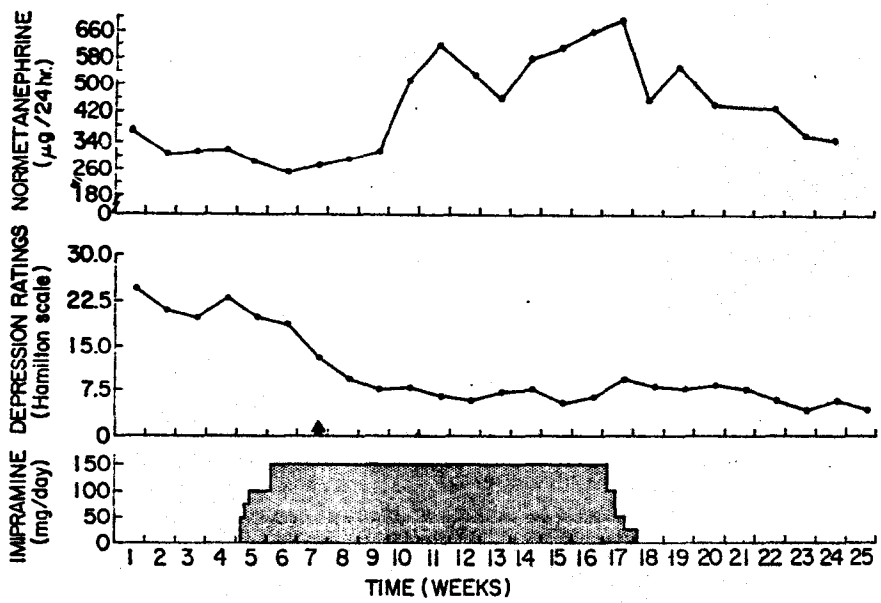
Fig. 19



Percentage of change in the plasma level of tyrosine as compared to the 8 AM level.

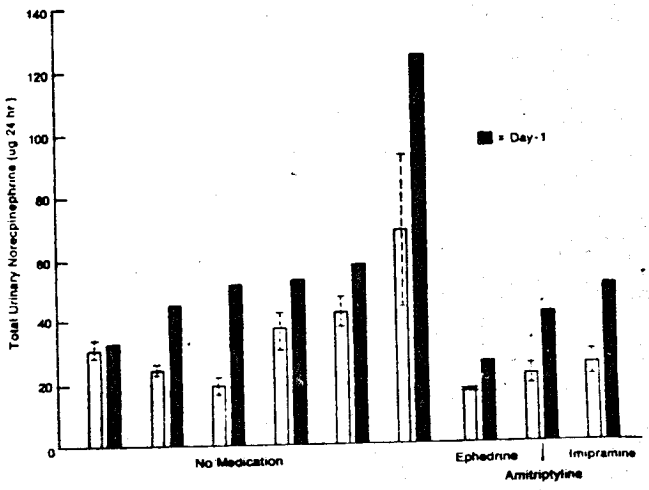
Benkert et al, 1971

Fig. 20



Clinical state and normetanephrine excretion in a depressed patient treated with imipramine. ↑, week of onset of definitive improvement determined by each of three independent raters. (Reproduced with permission from Schildkraut, J. J., Green, R., Gordon, E. K., and Durell, J., Amer. J. Psychiat., *125:* 690, 1966.)

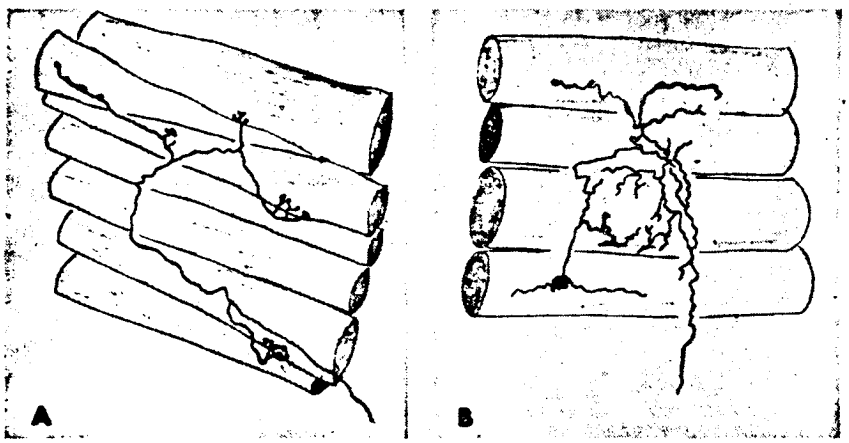
Fig. 21



Increase in norepinephrine one day prior to onset of mania.

Bunney et al, 1972

Fig. 22



(A) Patient 271. Camera lucida drawing of the distribution of one motor axon to five different muscle fibers. All branches end in well-developed nerve endings. (B) Patient 272, 33-year-old, black female: Acute schizophrenic, paranoid. Note the large numbers of immature sprouts with only two or three recognizable nerve endings.

Meltzer and Crayton, 1974

Fig. 23

	N	Mean	S.D.
Chronic anxiety	(54)	4.39	1.43
Agitated depression	(31)	3.37	1.22
Schizophrenia	(23)	3.13	1.31
Obsessional neurosis	(40)	2.71	1.12
Hysteria	(10)	2.48	0.97
Depersonalization	(10)	2.38	1.64
Phobic anxiety	(44)	2.13	0.91
Non-agitated depression	(64)	2.04	0.70
Personality disorder	(25)	1.88	0.57
Normal control	(60)	2.21	1.00

Mean "Basal" forearm blood flow (ml/100 ml/min) of 9 different diagnostic groups in rank order of magnitude and normal controls (Kelly and Walter 1970)

Kelly, 1971

Table I

REPORTS ON SUBSTANCES IN PLASMA OF PATIENTS WITH SCHIZOPHRENIA*

Investigator	*Year*	*Identifying Property*	*Protein Type*
Bergen	1963	Delays climbing time in rats	α^2
Frohman	1960	Raises the L/P ratio	α^2
		Amino acid increase	α^2
Ehrensvard	1967	Amine oxidase activity	α^2 or β^2
Krasnova	1965	Raises the L/P ratio	α^2
Lozovsky	1967	Raises the L/P ratio	α^2 or β^2
Ryan	1966	Hemolysis	?
Turner	1966	Hemolysis	?
Lideman	1967	Hemolysis	?
Lozovsky	1967	Hemolysis	?
Frohman	—	Hemolysis	?
Tikhonov	1967	Increases membrane permeability	β^2
Uzunov	1967	Increases membrane permeability	?
Lideman	1967	Increases membrane permeability	?
Romasenko	1967	Increases membrane permeability	?
Frohman	1968	Increases membrane permeability	α^2
Semenov	1967	Brain antigens	?
		Brain autoantibodies	?
Kuznetsova	1967	Brain autoantibodies	?
Kolyaskina	1967	Brain autoantibodies	?
Heath	1967	Brain autoantibodies	γ

*From Gottlieb, J. S., Frohman, C. E. and Beckett, P. G. S.: A theory of neuronal malfunction in schizophrenia. *Am. J. Psychiatry, 126*:149-156, 1969.

Table II

Mean norepinephrine, 5-HT, and 5-Hydroxyindoleacetic-acid levels in hindbrains of suicides and control subjects

	All Controls (ng/gm)	N^b	All Suicides (ng/gm)	N^b	Coronary controls (ng/gm)	N^b	Depressed subjects (ng/gm)	N^b
Norepinephrine	439	27	444	21	388	15	444	15
5-HT	234	25	213	23	218	13	211	16
5-Hydroxyindo-leacetic acid	1826[a]	28	1315[a]	23	1698[a]	15	1271[a]	16

[a] $p < 0.025$.
[b] N = number of subjects.

Coppen, 1974

TABLE III

Lumbar CSF-tryptophan concentration (ng per ml.) in patients with affective disorders and control subjects

Controls				Depressed patients			
No.	Sex	Age	CSF tryptophan	No.	Sex	Age	CSF tryptophan
1	F	47	200	1	F	61	172
2	F	67	622	2	F	34	196
3	F	66	575	3	F	71	296
4	F	38	395	4	M	24	277
5	F	43	390	5	F	58	269
6	M	66	295	6	F	41	227
7	M	55	380	7	F	74	305
8	M	58	760	8	M	42	170
9	M	43	280	9	F	56	520
10	M	58	390	10	F	63	166
11	M	24	466				
12	F	41	805				
13	M	70	560				
14	F	57	715				
Mean ± SE		52 ± 3.6	488 ± 50			52 ± 5.2	260 ± 34

Controls versus depressed patients: t 3.623, $p < 0.005$.

Coppen, 1974

TABLE IV

REFERENCES

AMKRAUT, A., SOLOMON, G.F., ALLANSMITH, M., et al: Immunoglobulins and improvement in acute schizophrenic reactions. Arch. Gen. Psychiatry 28: 673-677, 1973.

BENKERT, O. et al: Altered tyrosine daytime plasma levels in endogenous depressive patients. Arch. Gen. Psychiatry 25: 359-360, 1971.

BUCHSBAUM, M. et al: Average evoked response in bipolar and unipolar affective disorders: Relationship to sex, age of onset and monoamine oxidase. Biol. Psychiatry 7: 199-212, 1973.

BUNNEY, W.E., Jr., and FAWCETT, J.A.: Possibility of a biochemical test for suicidal potential: An analysis of endocrine findings prior to three suicides. Arch. Gen. Psychiatry 13: 232-239, 1965.

BUNNEY, W.E. et al: The switch process in manic-depressive illness. Arch. Gen. Psychiatry 27: 304-309, 1972.

COPPEN, A., ECCLESTON, E.G., and PEET, M.: Total and free tryptophan concentration in the plasma of depressive patients. Lancet 2/7820: 60-63, 1973.

COPPEN, A.: Serotonin in the affective disorders. In: Factors in Depression, N.S. Kline (ed.), 33-44. Raven Press, New York, 1974.

FAURBYE, A., and PIND, K.: Investigation of the occurrence of the dopamine metabolite 3, 4-dimethoxyphenylethylamine in the urine of schizophrenics. Acta Psychiatry Scand. 40: 240-243, 1964.

FRIEDHOFF, A.J., and VAN WINKLE, E.: Isolation and characterization of a compound from the urine of the schizophrenic. Nature 194: 1271-1272, 1963.

GIBBONS, J.L.: Steroid metabolism in schizophrenia, depression, and mania. In: Biochemistry, Schizophrenias, and Affective Illnesses, H.E. Himwich (ed.), 308-332. Williams and Wilkins, Baltimore, 1970.

GILMORE, T.D., and WILLIS, E.E.: Classroom performance and voice characteristics as measured by the contour sound spectogram: Preliminary report. Psychol. Rep. 27/1: 251-254, 1970.

GJESSING, L.R.: A review of periodic catatonia. In: Factors in Depression, N.S. Kline (ed.), 227-249. Raven Press, New York, 1974.

GOLDSTEIN, L. et al: Electro-cerebral activity in schizophrenics and non-psychotic subjects: Quantitative EEG amplitude analysis. Electroenceph. Clin. Neurophysiol. 19: 350, 1965.

GOTTLIEB, J., FROHMAN, G., and BECKETT, P.: A theory of neuronal malfunction in schizophrenia. Am. J. Psychiatry 126/2: 149-156, 1969.

GRUZELIER, J.H., and VENABLES, P.H.: Skin conductance orienting activity in a heterogeneous sample of schizophrenics. J. Nerv. Ment. Dis. 155: 277-287, 1972.

HEATH, R.G.: An antibrain globulin in schizophrenia. In : Biochemistry, Schizophrenias, and the Affective Illnesses, H.E. Himwich (ed.), 171-197. Williams and Wilkins, Baltimore, 1970.

HIMWICH, H.E.: Indoleamines and the schizophrenias. In: Biochemistry, Schizophrenias, and Affective Illnesses, H.E. Himwich,(ed.), 79-122. Williams and Wilkins, Baltimore, 1970.

KELLY, D.: Emotion and physiological changes in the arm. J. Psychosom. Res. 15: 445-450, 1971.

LESTRADET, H.: Les diabètes. La Recherche 51: 1051, December, 1974.

MANN, A., and LEHMANN, H.E.: The eosinophil level in psychiatric conditions. J. Can. Med. Assoc. 66: 52-58, 1952.

McKUSICK, V.A.: Inheritance and growth. In: Harrison's Principles Internal Medicine, M. Wintrobe et al (eds.), 6th Edition, 8-26. McGraw-Hill, New York, 1970.

MELTZER, H.Y., and CRAYTON, I.W.: Muscle abnormalities in psychotic patients. II. Serum GPK activity, fiber abnormalities, and branching and sprouting of subterminal nerves. Biol. Psychiatry 8/2: 191-208, 1974.

MULLER, H.F.: Generalized sharp activity in the electro-encephalogram of middle-aged and elderly psychiatric patients. J. Am. Geriatr. Soc. 17: 337-359, 1969

NOBLE, P., and LADER, M: The symptomatic correlates of the skin conductance changes in depression. J. Psychiat. Res. 9: 61-69, 1971.

PINCUS, J.H., and TUCKER, G.J.: Behavioral Neurology. Oxford University Press. London, 1974.

POLLIN, W.: The pathogenesis of schizophrenia. Arch. Gen. Psychiatry 27: 29-37, 1972.

SALETU, B., SALETU, M., and ITIL, T.: The relationships between psychopathology and evoked responses before, during and after psychotropic drug treatment. Biol. Psychiatry 6: 51, 1973.

SCHILDKRAUT, J., GREEN, R., GORDON, E., DURELL, J.: Normetanephrine excretion and affective state in depressed patients treated with imipramine. Am. J. Psychiatry 123/6: 690-700, 1966.

SCHILDKRAUT, J.H., HEELER, B.A., GRAB, E.L., KANTROWICH, J., and HARTMANN, E.: M.H.P.G. excretion and clinical classification in depressive disorders. Lancet 1: 1251-1252, 1973.

SJOSTROM, R., and ROOS, B.E.: 5-hydroxyindolacetic acid and homovanillic acid in cerebrospinal fluid in manic-depressive psychosis. Eur. J. Clin. Pharmacol. 4/3: 170-176, 1972.

SNEZHNEVSKY, A.V., and VARTANYAN, M.: The forms of schizophrenia and their biological correlates. In: Biochemistry, Schizophrenias, and Affective Illnesses, H.E. Himwich (ed.), 1-28. Williams and Wilkins, Baltimore, 1970.

SPECK, L.B., DIM, B., and MERCER, M.: Visual evoked responses of psychiatric patients. Arch. Gen. Psychiatry 15: 59-63, 1966.

STABENAU, J.R., GRAVELING, C.R., and DALY, J.: The pink spot 3, 4-dimethoxyphenylethylamine common tea, and schizophrenia. Am. J. Psychiatry 127: 611-616, 1970.

WILSON, A., and WILSON, A.S.: Psychophysiological and learning correlates of anxiety and induced muscle relaxation. Psychophysiology 6/6: 740-748, 1970.