Biochemical Research into Schizophrenia in Relation to Pink Spot Excretion

A. Pauline Ridges, Ph.D., M.Sc, A.R.I.C.

The Aetiology of Mental Illnesses

During the 19th century concepts concerning the aetiology of mental illnesses were changing. The idea that they were due to a disturbance in the chemistry of the body was gradually developing, (Conolly[1] 1856 and Thudicham[2] 1884) but despite the advanced and progressive ideas of psychiatrists a hundred years ago, today our understanding of the aetiology of schizophrenia appears to be no more clear than it was then. Freud[3] said, *'The future may teach us how to exercise a direct influence by means of particular chemical substances on the apparatus of the mind* but it is not for this viewpoint that he is remembered.

In this century psychiatry has largely followed schools of thought which, by considering illnesses in abstract terms, have avoided the basic difficulty of requiring a knowledge of the neurobiological basis of cerebral functioning. Although this lack of knowledge has been a limitation, it has not prevented biochemical investigations into the aetiology of schizophrenia, particularly with the object of detecting metabolic

This paper was presented at the joint meeting of The American Schizophrenia Association, The Canadian Schizophrenia Association and The Schizophrenia Association of Great Britain; London, England, September 28-30, 1971.

errors in body fluids and tissues, but there can be few areas of biochemical research which abound with as many conflicting and contradictory reports as that concerned with schizophrenia.

Many of the investigations have not been documented in sufficient detail to enable a proper assessment of them to be made and there is a great need for well controlled and scientifically designed experiments to clarify the position in a number of areas.

In this paper reference is made to selected topics of research which are not exhaustive nor even proved to be relevant to the aetiology of schizophrenia but which appear to merit further attention. In considering these it is important to emphasize two points.

Firstly, that the terms used in psychiatry have evolved with the structure and practice of this discipline and lack a precise definition. Such is the case when referring to schizophrenia, Richter.[4] It can be used with such different meanings that in any research, it is necessary to qualify the term, as well as one can in the absence of tests—to specifically diagnose the condition and quantify the symptoms.

Secondly, it is important to appreciate that there are many factors whose effect on body chemistry must be considered before differences between schizophrenics and other people can correctly be attributed to the disease, Horwitt[5] and Kety.[6] Variables, such as differences in sex, diet or therapy have in the past influenced findings which were purported to be associated with the aetiology of the disease. In this symposium Mosher (page 60) has cited two investigations which serve as examples where failure to take account of a vital factor has resulted in an incorrect interpretation being put on the data.

A Biochemical Derangement

Today there is still a divergence of opinion about the contribution of genetic, biochemical and environmental factors to the aetiology of schizophrenia but cannot be logically disputed that schizophrenia is the result of a biochemical derangement.

Although the details are obscure there is considerable evidence to support the belief that schizophrenia has a genetic basis, (Shield[7]) also it is known that metabolism is under the influence of genes Stanburg.[8] Genes exert their effects by directing the synthesis of enzymes, (Beadle and Tatum[9]) which can exist in different molecular forms known as isoenzymes and other proteins.

Environmental factors also influence the body chemistry through the nervous system. The weight which is placed on genetic as distinct from environmental factors is empirical. For example, in vitamin deficiency diseases emphasis is placed on environmental factors because everyone has the genetic disposition to develop the disease (but only if the diet is sufficiently lacking in vitamins); in contrast emphasis is put on genetic factors in phenylketonuria where the genetic defect is comparatively rare and the aggravating agency, dietary phenylalanine, is universal in the normal diet.

In between these extremes there are many conditions, often common ones such as schizophrenia, which are more difficult to understand because people may have the appropriate genetic makeup without developing the condition.

It would seem that some change is produced by an environmental factor on a biochemical pathway which because of a genetic defect(s), is limited in the extent to which it can adjust itself. Because of this other routes of metabolism become operative and thus the environmental factor can trigger off a chain of events.

At some point changes occur in the central nervous system which result in the production of schizophrenic symptoms. It appears that the brain and nervous system have a limited way of responding to metabolic variations so that a number of basically different defects may be expressed finally through common pathways.

It is feasible that in schizophrenia a number of different conditions may be ultimately differentiated, all of which give rise to a common symptomatology. This would be consistent with the idea that schizophrenia is not a discrete disease entity. A general hypothesis stating that schizophrenia is the result of metabolic defects associated with specific isoenzyme activity could be formulated.

DMPE Present in Schizophrenia

It would be an advantage if individuals in the population having the genetic constitution to develop schizophrenia could be identified. It was from this viewpoint that our investigations were started following a report, (Friedhoff[10]) that in a small series of people there was a substance, stated to be DMPE, present in the schizophrenics but not in normal individuals.

Investigations of schizophrenics and their families showed that by our methods we were unable to distinguish between the unaffected relatives of schizophrenics and

other mentally normal individuals, Bourdillon and Ridges.[11] However, we were able to demonstrate, under double blind conditions, that there was material in the urine of some schizophrenics which could not be found in patients with other psychiatric diagnoses nor in normal individuals, Bourdillon et al.[12] Using a large number of patients this association was shown to be highly significant. (See table I.)

The material which was located as a pink spot on chromatograms was carefully defined in relation to its properties on solvent extraction at a specified pH, ultraviolet absorption spectrum, R_f in various solvent systems and staining reactions. Together these characteristics were not considered to constitute a positive identification, although other workers were ready to identify pink spot as DMPE and to equate other pink staining materials having distinct characteristics with 'pink spot', Williams,[13] Boulton, et al.,[14] Stabenau, et al.[15]

As with other biochemical research into schizophrenia, contradiction and confliction of evidence has made it difficult for workers not acquainted with the field to ascribe a definite validity and value to the findings. In addition to variables already mentioned, methodology has undoubtedly contributed to the confusion.

We have compared our methods with those used by other workers and have found that those who reported positive findings for normal urine were using procedures (Takesada et al.[16]) which separated more material isographic with DMPE on chromatograms than did our method. This material can be separated from pink spot and when this is done pink spot is only found to be present in schizophrenics. Our findings indicate that the material responsible for these reports of positives in urines from control subjects is of dietary origin.

Pink Spot Found Most in Acutely Disturbed Patients

Throughout our studies our results have been consistent. Our data has been subjected to a multifactorial analysis which in-

TABLE I
INCIDENCE OF PINK SPOT

	Pink Spot Rating *Impossible*	*Positive*	*Negative*	*to assess*
	Totals			
Mentally normal individuals	1	391	0	392
*Psychiatric patients, mostly acute and not on drugs. (All selected and rated by same psychiatrist.)**				
Schizophrenics (excluding paranoid schizophrenics)	4	12	11	67
Paranoid schizophrenics	2	15	0	17
Non-schizophrenics	0	16	1	17
Psychiatric patients, more chronic than in above group. (Selected by case sheet diagnosis-large proportion on drugs.)				
Non-paranoid schizophrenics	20	30	19	69
Paranoid schizophrenics	2	54	6	62
Schizophreniform syndromes	5	58	25	88
Non-schizophrenics	1	68	8	77

* Non-paranoid vs. Paranoid Chi^2 — 20.18; d.f. = 1; $p < 0.001$ Non-paranoid vs. Control $p = 8.06 \times 10^{-32}$
Non-paranoid with paranoid $Chi^2 = 19.16$; d.f. = 1; $p < 0.001$ Non-paranoid with non-schizophrenics, $Chi^2 = 27.05$; d.f. = 1; $p < 0.001$

eluded as variable, urine pH and volume, creatinine excretion, presence of other materials on the chromatogram, hospital, age, sex, duration of hospitalization and symptomatology, etc. Although we have paid much attention to the possibility that other factors may be responsible for our findings, we have not been able to explain the association which we found in terms of any factors other than schizophrenia, Bourdillon and Ridges,[17] Ridges et al.,[18] Ridges and Harper,[19] and Ridges.[20]

Our initial studies comprised:

(1) Mentally normal individuals including hospital patients with general medical conditions, liver disease and chronic neurological conditions.

(2) Schizophrenics, many of whom were acutely disturbed and who had never received drugs or who were not receiving drugs at the time of testing (expt. par. 1). All were carefully selected and assessed by a single psychiatrist.

(3) Patients selected by case sheet diagnosis. This group, whose diagnoses had been made by a number of different psychiatrists, was divided into schizophrenics, schizophreniform syndromes (where an alternative diagnosis to schizophrenia had been raised) and other diagnoses (expt. par. 2).

These and other studies have led us to make the following generalizations with regard to the type of patients who were pink spot positive. Pink spot was found most frequently in acutely disturbed patients, especially those having Schneider's first rank symptoms, (Schneider[21]) table II and rarely in patients whose conditions had become chronic.

Although pink spot was excreted by some paranoid schizophrenics it was most commonly associated with those schizophrenics who did not display any paranoid symptoms. Consequently the incidence of pink spot excretion varies according to the

TABLE II

PINK SPOT EXCRETION IN SCHIZOPHRENICS IN RELATION TO SCHNEIDER'S FIRST RANK SYMPTOMS

Schneider rating	*Pink Spot status*			
	Positive	*Negative*	*Impossible to assess*	*Totals*
Positive	35	11	6	52
Negative	7	16	4	27
Impossible to assess	4	0	1	5
TOTALS:	46	27	11	84

population of schizophrenics included in an investigation.

Drug Therapy Reduces Chances of Finding Pink Spot

Pink spot has been found in the urine of patients who are known never to have received any therapy. Its excretion is influenced by the drug therapy of the patients in that therapy reduces the chances of finding pink spot in the urine, Ridges and Harper.[22] This is not merely because of the increased difficulty in interpreting chromatograms due to the presence of drug metabolites in much greater amounts than pink spot (as reflected in the large number of cases reported as "impossible to assess" (table I), longitudinal studies of patients who excreted pink spot prior to any medication have been found to cease to do so within days of the initiation of therapy. We have no evidence to support the view that DMPE or drug metabolites are responsible for our findings (Ridges and Harper,[19] Bourdillon and Ridges[23]) as some workers have suggested, Steinberg and Robinson,[24] and Seigel and Tefft.[25]

To date it has not been possible to positively identify pink spot, a major difficulty being the shortage of samples from acutely disturbed and previously untreated patients. It is known that the pink spot material from paper chromatograms, when investigated by more sophisticated

techniques can be resolved into **a** number of distinct substances which are methylated and methoxylated compounds chemically similar to the catecholamines.

In a pilot study we have found that in schizophrenics who excrete pink spot, larger amounts of dopamine than normal appear to be excreted in their urine and levels of dopamine show considerable fluctuation.

It seems, therefore, that there may be in the schizophrenics who excrete pink spot, some differences in the metabolism of catecholamines. In view of our findings and known facts such as the intimate involvement of catecholamines in the transmission of nerve impulses, and the psychosis produced in some individuals by the administration of L-dopa, we are of the opinion that investigation of catecholamine metabolism in schizophrenia merits further attention.

An Elevation of Catecholamine Excretion in Acute Schizophrenia; No Such Change in Chronic Schizophrenia

Although there is suggestive evidence that a relationship exists between catecholamine metabolism and mental illness, a precise relationship has not been demonstrated, (Bourdillon and Ridges,[23] Kety,[26]-[27] Stern and McDonald[28]). Emotional stress can increase catechol excretion in mentally normal individuals. There is some evidence to indicate that there may be an elevation of catecholamine excretion in acute shizophrenia whereas no such changes occur in chronic schizophrenia, Bergsman.[29]

Other workers have demonstrated that in schizophrenia there is an increased excretion of catecholamines during periods of increased motor activity, anxiety and tension (Bertlet et al.,[30] Brune and Pscheidt,[31] Brune et al.,[32] Pscheidt et al.[33]) as if the level of urinary catechol is governed by sympathetic activity. Emotional factors could modify catecholamine excretion whilst the overall metabolism might still

A. Pauline Ridges, Ph.D., M.Sc, A.R.I.C.
Senior Lecturer in
Biochemical Psychiatry
Department of Psychiatry
University of Liverpool
Life Sciences Building
Crown Street
Liverpool 7, England

appear normal in schizophrenics.

Other workers, (Mattock et al.[34]) studying the dynamic aspects of catecholamine metabolism by measuring the levels of adrenaline, noradrenaline, dopamine, metaneph-rine and normetanephrine and their conjugates in a single urine sample, concluded that dopamine is synthesised normally in schizophrenia but is metabolised to give abnormally high concentrations of noradrenaline and in turn adrenaline. The increased concentration of adrenaline may produce stimulation of the processes leading to conjugation and possibly removal of the excess adrenaline by an abnormal process.

Another report states that a route of di-hydroxyphenylalanine metabolism operative particularly in pathological conditions involves transamination and methylation, (Smith[35]). There exists the possibility that in schizophrenia the stress mechanism may be faulty and that an abnormal metabolite may be formed.

Changes in Catecholamine Metabolites

Such changes in catecholamine metabolites may be parallelled by alterations in indolealkylamine metabolism and it would be of considerable value to consider both classes of compounds in relation to each other for both may be significant in the pathogenesis of schizophrenia, Tonimukai, et al.[36] Evidence has been provided which indicates that these indolealkylamines are

deranged in schizophrenia and bufotenin has been reported to be found in the urine of schizophrenics. Other workers have also claimed to have found this substance, Bum-pus and Page,[37] Fischer and Spatz.[38] One can substantiate the argument with a variety of hypotheses and pieces of evidence, that because of a deranged catecholamine metabolism a toxic metabolite is formed. Many of these have centered around the fact that methylation reactions play an important part in the metabolism of catecholamines, and that hallucinogens are themselves methylated compounds and that the administration of monoamine oxidase inhibitors and methyl donors, (Brune and Himwich,[39] Pollin et al.[40]) causes a worsening of schizophrenic symptoms.

Stein and Wise[41] have postulated that in schizophrenia there is a pathological gene which by impairment of the enzyme dopamine B-hydroxylase leads to the aberrant metabolism of dopamine to 6-hydroxydopa-mine. This is known to be a toxic substance and electron microscope studies reveal that it causes a selective destruction of sympathetic nerve terminals, but it has no action on dopaminergic terminals. Such damage would be irreversible. Electron microscope studies of schizophrenic brain could clarify whether this situation does in fact exist for it is widely stated that in schizophrenia there is no visible pathology, nor do we really know whether there is irreparable damage in schizophrenics.

It is a striking fact that schizophrenia is frequently evoked by the conditions of a stressful nature which also activate the adrenal pituitary system. Activation of this system does not involve tissue damage and is in itself suggestive that in schizophrenia there is an imbalance of metabolism. Because of the delicate equilibrium between the endocrine organs a disturbance in the adrenal function could have widespread repercussions including for example the changes in carbohydrate metabolism which have been reported in schizophrenia.

When labelled dopamine is administered 97.2%, (Goodall and Alton[4]-) can be accounted for although the metabolites do not include the aminochromes which are almost certainly capable of being formed *in vivo,* for all the necessary enzyme systems are known to exist. No methods at present exist for the accurate estimation of these compounds. It is interesting to note (see Altschule page 8 of this symposium) that red blood cells from schizophrenics are lysed *in vitro* by aminochromes.

The Adrenochrome Hypothesis Has Evolved Into The Aminochrome-melanin Hypothesis

It has been suggested that in schizophrenia there is an abnormal melanogene-sis, Greiner.[43] This increased pigmentation in schizophrenia is not merely an effect of phenothiazine administration.

In the body dopa oxidase and copper ions are required for the conversion of di-hydroxyphenylalanine to melanin and the reaction is influenced by catecholamines and the pineal hormone melatonin, Greiner and Nicholson.[44] It could be reasoned that D-penicillamine which is a copper-chelat-ing agent might cause a decreased pigmentation and also an improvement in the schizophrenic symptoms. This is supported by the findings of some workers, (Nicholson et al.,[45] Helmchen et al.,[46] Maltke and Adler[47]) whereas others, (Hollister et al.,[48] Walshe,[49] and Affleck et al.[50]) concluded that D-penicillamine was unlikely to be of clinical value.

The Copper Containing Enzyme Caerulo-plasmin, Implicated in Schizophrenia

The copper containing enzyme caerulo-plasmin has also been implicated in schizo-phrenia. It has been reported, (Akerfeldt[51]) to be present in higher concentrations in the plasma of schizophrenic patients than in normals but the validity of this has been doubted, Wurtman, et al.[52] The oxidation

of noradrenaline and 5-hydroxytryptamine by caerupoplasmin has been studied *in vitro* in the presence of urinary extracts from schizophrenics, (Barrass et al.[53]) and in the presence of LSD which is known to have the effect *in vivo* of elevating brain 5-hydroxytryptamine levels and depressing brain catecholamine levels. The oxidation of noradrenaline was accelerated by the schizophrenic extracts.

It was suggested that the active factor in the schizophrenic urine might be a small heteropeptide containing a catecholamine residue. Bergen[54] also considered that a small molecule having properties resembling a catecholamine was associated with a plasma factor in schizophrenics. The relationship between these factors and pink spot is obviously of great interest, as is the relationship between the various plasma factors which have been reported, Heath and Krupp,[55] Frohman et al.[56] and cooperative study.[57]

Connection Between Coeliac Disease and Schizophrenia Suggested

At the present time insufficient attention has been given to other observations which might be of importance in an understanding of schizophrenia. The suggestion by Dohan[58] that a connection exists between coeliac disease and schizophrenia is supported by the finding of a more frequent association of these in the same person and possibly the same family than would be expected by chance, (Dohan[59]) the decreased incidence of schizophrenia in wartime associated with the shortage of grain, (Dohan[60]) and the shorter length of stay in a hospital ward for patients maintained on a gluten free diet, Dohan.[61]

Such a relationship would underline the possible importance of the intestine in the aetiology of schizophrenia which has been emphasized, (Buscaino[62]) particularly with regard to the permeability of the intestine
to small molecules such as peptides and the absorption of vitamins.

The successful use of vitamins in the treatment of schizophrenia, (Hoffer[63]) has been refuted, (Ban and Lehmann,[64] Kline et al.[65]). However the conditions laid down in the initial report have not been reproduced in detail. The length of time and level of administration of vitamins and the condition and duration of illness of the patient must obviously be considered if any valid comparisons are to be made and conclusions drawn. It should be remembered that vitamins should be "regarded as substances which bearing a quantitative relationship to the total metabolism, albeit one which does not dispose of large amounts of energy in its own right. Nevertheless it is upon this cryptic metabolic cycle of the vitamins involved in carbohydrate respiration that the dynamically greater and metabolically more obvious cycle of carbohydrate metabolism is supported," Gould.[66]

Today No Unified Theory Reconciles Available Evidence

At the present time there is no unified theory which will reconcile the available evidence. The biochemical parameters which are suspect in schizophrenia are numerous, some could be primary lesions and others secondary adjustments in the functioning of the body.

It is now feasible that with present methods, pursuing the most detailed investigation of patients, under carefully controlled and defined conditions, devised to obtain a biochemical profile, our knowledge of schizophrenia should progress.

The position is complex but not hopeless. Schizophrenia is a soluble problem which will yield to intensive research of high quality, so that future generations may marvel how it was, that in the 20th century the cause of schizophrenia remained a mystery for so long.

REFERENCES

1. CONOLLY, J.: The Treatment of the Insane Without Mechanical Restraints. Smith, Elder & Co. London 1856.
2. THUDICHUM, J. W. L.: A Treatise on the Chemical Constitution of the Brain. Balliere, Tyndall & Cox. London 1884.
3. FREUD, S.: An Outline of Psychoanalysis. 1938 Edn. Trans. J. Strachey Publ. Hogarth 1949.
4. RICHTER, D.: Biochemical Aspects of Schizophrenia. In: Schizophrenia, Somatic Aspects. London, Pergamon Press, p. 53 1957.
5. HORWITT, M. K.: Critique on Studies of Metabolism in Schizophrenia. In: Recent Advances in Biological Psychiatry. J. Wortis (Ed.) 5:257. Plenum Press, New York, 1963.
6. KETY, S. S.: Dietary Factors and Schizophrenia. In: Chemical Influences on Behavior. R. Porter and J. Birch (Eds.): Ciba Foundation Study Group. 35:76. Churchill, London 1970.
7. SHIELDS, J.: Schizophrenia: Summary of the Genetic Evidence. J. Psychiat. Res. 6 (Suppl. 1) 95, 1968.
8. STANBURY, J. B., WYNGAARDEN, J. B. and FREDERICKSON, D. S.: Inherited Variation and Metabolic Abnormality. In: Metabolic Basis of Inherited Disease. J. B. Stanbury, J. B. Wyngaarden and D. S. Frederickson (Eds.) 11:3, 2nd Edition, McGraw Hill, 1966.
9. BEADLE, G. W. and TATUM, E. L.: Genetic control of biochemical reactions in neurospora. Proc. Nat. Acad. Sci. U.S. 27:499, 1941.
10. FRIEDHOFF, A. J. and VAN WINKLE, E.: Isolation and characterisation of a compound from the urine of schizophrenics. Nature (Lond.) 194:897, 1962.
11. BOURDILLON, R. E. and RIDGES, A. P.: 3,4-Dimethoxyphenylethylamine in Schizophrenia? In: Amines and Schizophrenia. H. E. Him-wich, S. S. Kety and J. R. Smythies (Eds.): Pergamon Press, Oxford, p. 43 1966.
12. BOURDILLON, R. E., CLARKE, C. A., RIDGES, A. P., SHEPPARD, P. M., HARPER, P. and LESLIE, S. A.: 'Pink spot' in the urine of schizophrenics. Nature (Lond) 208:453, 1965.
13. WILLIAMS, C. H.: Pink spot excretion in schizophrenia. Proc. Roy. Soc. Med. 60:558, 1967.
14. BOULTON, A. A., POLLITT, R. J. and MAJER, J. R.: Identity of a urinary 'pink spot' in schizophrenia and Parkinson's disease. Nature (Lond) 215:132, 1967.
15. STABENAU, J. R., CREVELING, C. R. and DALY, J.: The pink spot, 3,4-dimethoxyphenylethyla-mine, common tea and schizophrenia. Amer. J. Psychiat. 127:611, 1970.
16. TAKESADA, M., KAKIMOTO, Y., SANO, I. and KANEKO, Z.: 3,4-dimethoxyphenylethylamine and other amines in the urine of schizophrenic patients. Nature (Lond) 199:203, 1963.
17. BOURDILLON, R. E. and RIDGES, A. P.: The Pink Spot. Lancet 1:429, 1966.
18. RIDGES, A. P., BOURDILLON, R. E., LESLIE, S. A. and HARPER, P.: 'Pink Spot' and schizophrenia. Psychiat. Clin. 1:44, 1968.
19. RIDGES, A. P. and HARPER, P.: Pink Spot—Is it a drug artefact? Psychiat. Clin. 3:101, 1970.
20. RIDGES, A. P.: Pink Spot, 3,4-dimethoxy-phenylethylamine, common tea and schizophrenia. Amer. J. Psychiat. 128:122, 1971.
21. SCHNEIDER, K.: Clinical Psychopathology. (Trans. M. W. Hamilton). Grune & Stratton, New York, 1959.
22. RIDGES, A. P. and HARPER, P.: Urinary chrom-atographic abnormalities in schizophrenia and Parkinson's disease with special reference to their relationship to drug treatment. In: Progress in Neurogenetics 1. Excerpta Med. Int. Congr. Ser. 175, p. 442, 1969.
23. BOURDILLON, R. E. and RIDGES, A. P.: Cate-cholamines and Schizophrenia. In: Biochemistry, Schizophrenia and Affective Illnesses. H. E. Himwich (Ed.). Williams & Wilkins, Baltimore, p. 123, 1970.
24. STEINBERG, H. R. and ROBINSON, J.: Nor_2-Chlorpromazine sulphoxide and 3,4-dimeth-oxyphenylethylamine. Nature (Lond) 217: 1054, 1968.
25. SIEGEL, M. and TEFFT, H.: 'Pink Spot' and its components in normal and schizophrenic urine. J. Nerv. Ment. Dis. 152:412, 1971.
26. KETY, S. S.: Biochemistry and mental function. Nature (Lond) 207:1252, 1965.
27. KETY, S. S.: Catecholamines in neuropsychiatric studies. Pharmacol Rev. 18:787, 1966.
28. STERN, J. A. and MCDONALD, D. G.: Physiological correlates of mental disease. In: Ann. Rev. of Psychology. P. R. Famsworth, O. McNemar and Q. McNemar (Eds.): 16:225, 1965.
29. BERGSMAN, A.: The urinary excretion of adrne-laine and noradrenaline in some mental diseases. A clinical and experimental study. Acta Psychiat. Neurol. Scand. 134 (Suppl. 133): 11, 1959.
30. BERLET, H. H., MATSUMOTO, K., PSCHEIDT, G. R. SPAIDE, J., BULL, C. and HIMWICH, H. E.: Biochemical correlates of behavior in schizophrenic patients. Arch. Gen. Psychiat. 13:521, 1965.

31. BRUNE, G. G. and PSCHEIDT, G. R.: Correlations betwen behavior and urinary excretion of indole amines and catecholamines in schizophrenic patients as affected by drugs. Fed. Proc. 20:889, 1961.
32. BRUNE, G. G., PSCHEIDT, G. R. and HIMWICH, H. E.: Different responses of urinary trypta-mine and of total catecholamines during treatment with reserpine and isocarboxazid in schizophrenic patients. Int. J. Neuropharmacol. 2: 17, 1963.
33. PSCHEIDT, G. R., BERLET, H. H., BULL, C, SPAIDE, J. and HIMWICH, H. E.: Excretion of catecholamines and exacerbation of symptoms in schizophrenic patients. J. Psvchiat. Res. 2: 163, 1964.
34. MATTOCK, G. L., WILSON, K. L. and HOFFER, A.: Catecholamine metabolism in schizophrenia. Nature (Lond) 213:1189, 1967.
35. SMITH, P.: Metabolism of dihydroxyphenylala-nine in human subjects. Nature (Lond) 213: 802, 1967.
36. TONIMUKAI, H., ClNTHER, R., SPAIDE, J., BUENO, J. and HIMWICH, H. E.: Detection of psychotomimetic N,N-dimethylated indolea-mines in the urine of schizophrenic patients. Brit. J. Psychiat. 117:421, 1970.
37. BUMPUS, F. M. and PAGE, I. H.: Serotonin and its methylated derivatives in human urine. J. Biol. Chem. 212:111, 1955.
38. FISCHER, E. and SPATZ, H.: Quantitativer Nachweis einer vermehrten Bufoteninausschei-dung im Urin Schizophrener. Arch. Fur Psychiatric und Zeitschrift. f.d. ges. Neurologie 211:241, 1968.
39. BRUNE, G. G. and HIMWICH, H. E.: Biogenic Amines and Behavior in Schizophrenic Patients. In: Recent Advances in Biological Psychiatry. J. Wortis (Ed.), Plenum Press, New York, Vol. 5, p. 144, 1962.
40. POLLIN, W, CARDON, P. V. and KETY, S. S.: Effects of amino acid feeding in schizophrenic patients treated with iproniazid. Science 133: 104, 1961.
41. STEIN, L. and WISE, C. D.: Possible etiology of schizophrenia: Progressive damage to the noradrenergic reward system by 6,hydroxy-dopamine. Science 171:1032, 1971.
42. GOODALL, McC and ALTON, H.: Metabolism of 3-hydroxvtyramine (Dopamine) in human subjects. Biochem. Pharmacol. 17:905, 1968.
43. GREINER, A. C: Schizophrenia, melanosis iactrogenic—congenital defect? Dis. Nerv. Svst. 29:14, 1968.
44. GREINER, A. C. and NICHOLSON, G. A.: Schizophrenia—melanosis, cause or side effects? Lancet 2:1165, 1965.
45. NICHOLSON, G. A., GREINER, A. C, McFAR-LANE, W. J. G. and BAKER, R. A.: Effect of penicillamine on schizophrenic patients. Lancet 2:344, 1966.
46. HELMCHEN, H., HIPPIUS, H., HOFFMANN, I. and SELBACH, H.: D-pennicillamin in der Schizophrenie-Behandlung. Nervenarzt 38:218, 1967.
47. MALTKE, D. J. and ADLER, M.: Mode of action of D-penicillamine in chronic schizophrenia. Dis. Nerv. Syst. 32:388, 1971.
48. HOLLISTER, L. E., MOORE, F. F., FORREST, F. and BENNETT, J. L.: Antipyridoxine effect of D-penicillamine in schizophrenic men. Amer. J. Clin. Nutr. 19:307, 1966.
49. WALSHE, J. M.: A study of copper transport in schizophrenia. In: Molecular Basis of Some Aspects of Mental Activity. O. Walaas (Ed): Academic Press, London, Vol. 2, p. 175, 1967.
50. AFFLECK, J. W., COOPER, A. J., FORREST, A. D., SMYTHIES, J. R. and ZEALLEY, A. K.: Penicillamine and schizophrenia—a clinical trial. Brit. J. Psychiat. 115:173, 1969.
51. AKERFELDT, S.: Oxidation of N,N-dimethyl-p-phenylenediamine by serum from patients with mental disease. Science 125:117, 1957.
52. WURTMAN, R. J., FRANK, M. M. and ALTSCHULE, M. D.: The oxidative activity of blood serum in schizophrenic and manic depressive psychosis. Arch. Intern. Med. 102: 790, 1958.
53. BARRASS, B. C, COULT, D. B., DRYSDALE, A. C and MARJOT, D. H.: Inhibition and activation of caeruloplasmin by extracts from the urine of schizophrenic patients. Biochem. Pharmacol. 19:1675, 1970.
54. BERGEN, J. R.: Possible relationship of a plasma factor to schizophrenia. Trans. N.Y. Acad. Sci. 28:40, 1965.
55. HEATH, R. G. and KRUPP, I. M.: Schizophrenia as a specific biologic disease. Amer. J. Psychiat. 124:1019, 1968.
56. FROHMAN, C. E., HARMISON, C. R., ARTHUR, R. E. and GOTTLIEB, J. S.: Conformation of a unique plasma protein in schizophrenia. Biological Psychiatry 3:113, 1971.
57. Cooperative Study: Plasma factors in schizophrenia. Arch. Gen. Psychiat. 18:471, 1968.
58. DOHAN, F. C: Cereals and schizophrenia, data and hvpothesis. Acta Psychiat. Scand. 42:125, 1966.'
59. DOHAN, F. C: Coeliac disease and schizophrenia. Lancet 1:897, 1970.
60. DOHAN, F. C: Wartime changes in hospital admissions for schizophrenia. Acta Psychiat. Scand. 42:1, 1966.
61. DOHAN, F. C, GRASBERGER, J. C, LOWELL, F. M., JOHNSTON, H. T. and ARBEGAST, A. W.: Relapsed schizophrenics: More rapid improvement on a milk and cereal-free diet. Brit. J. Psvchiat. 115:595, 1969.
62. BUSCAINO, V. M.: Biologia E terapia della schizophrenia. Acta. Neurol. 25:1, 1970.

Continued on page 36