DISTURBANCES OF SERINE AND GLYCINE METABOLISM AS A CAUSE OF EPISODIC ACUTE POLYMORPHOUS PSYCHOSES

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INTRODUCTION

Psychiatrists are frequently confronted with psychoses that are difficult to classify.

Many forms of these atypical psychoses have been described in European literature. They often have an acute onset and a tendency towards complete remission, albeit with an episodic course. Rich, multiform symptomatology is noted sometimes in addition to altered states of consciousness.

In patients with a grossly impaired consciousness the psychiatrist has also to consider whether such a psychosis is due to organic factors or is functional (1).

Even when morphologically demonstrable organic factors are excluded, the possibility of a reaction of the brain to subtle toxic factors disturbing the normal physico-chemical equilibrium without causing cellular damage has to be taken into account.

An intermittent production of such toxins in the brain or the liver has been an attractive concept for many researchers to understand and account for the endogenous functional psychoses (2).

In this thesis an attempt is made to provide clinical evidence for the endogenous synthesis of toxic factors which are causally related to some types of the atypical psychoses. The findings have led to a new classification of the group of poorly defined and previously unclassifiable psychoses.

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CHAPTER I.

A CASE HISTORY: INVOLVEMENT OF DYSMETHYLATION AS A POSSIBLE CAUSE FOR THE PSYCHOSIS

Two highly controversial problems of clinical psychiatry are discussed in this chapter.

The first problem concerns the old idea that certain forms of insanity, in particular the schizophrenic psychoses, are caused by endogenously produced toxins (1).

The second problem, which has been discussed for almost a century, is the question whether a separate group of psychoses might exist that, though the clinical picture of these psychoses comprises a mixture of affective and alleged schizophrenic symptoms, is not a variety of Manic-Depressive Illness or Schizophrenia.

The case of one particular patient, described below, led us to the idea that a psychotic state which lacked the classical symptoms of organic brain dysfunction, especially impairment of consciousness, could be caused by the endogenous formation of a well-known type of psychotoxin.

The historical roots of this idea go back to the first decades of this century. As early as 1921 the urines of acute schizophrenics were found to form black precipitates with silver nitrate. This black reaction of amino substances was not found in urines of controls. In the following decades abnormal levels of indole compounds were discovered in the urine and serum of chronic schizophrenics (1).

Transmethylation hypothesis of schizophrenia

The transmethylation hypothesis, first proposed by Osmond and Smythies in 1952 (2) was a major advance in research into the aberrant biochemistry of schizophrenia.

The resemblance between mescaline and noradrenaline was stressed by these

authors who suggested that schizophrenia resulted from the faulty methylation of excessive catecholamines, released under stress.

In this they followed Harley-Mason's suggestion that 3,4-dimethoxyphenyl-ethylamine (DMPEA) was a likely candidate as a psychotogenic substance, for it was reported to be highly potent in producing catatonia in animals. Thus, instead of normal N- and O-methylation, abnormal O-methylation of catecholamines would occur in schizophrenia. As a result of their studies, it was realized that most of the hallucinogens had an indole nucleus. In order not to abandon the original hypothesis, it was assumed that the side chain of mescaline readily fused by its aminogroup formed an indole compound.

The chance observation that somewhat deteriorated adrenaline solutions gave unfavourable mental reactions resulted in the notion that this had to be due to a derivative of adrenalin, adrenochrome which has also an indole structure.

Administration of adrenochrome did evoke typical psychedelic experiences (3, 4). However, the adrenochrome hypothesis has since been abandoned as adrenochrome can not be detected in body fluids of schizophrenics or normals (5, 6), and catecholamines present in or added in physiological quantities to plasma are found to be stable in plasma from both normal and schizophrenic subjects (7, 8).

When another class of hallucinogens was detected, namely the methylated derivatives of serotonin, N,N-dimethyltryptamine, 5-methoxydimethyltryptamine and 5-methoxytryptamine (9, 10, 11) the original hypothesis was extended to the abnormal N-methylation of indolamines. A hypothesis that found considerable substantiation when enzymatic formation of such substances was demonstrated (12, 13, 14, 15).

Support for a faulty methylation of catecholamines or indolamines was acquired through the experiments of Pollin et al., loading chronic schizophrenic patients with the methyldonor substance methionine combined with a MAO-inhibitor (16). Exacerbations of psychotic symptoms or a superimposed toxic psychotic state were noted in many chronic schizophrenic patients (approx. 58%) by independent groups of investigators (17, 18, 19).

Large doses of methionine (5-40 gram/70 kg/day) were administered for periods of one week up till two months. Even when no MAO-inhibitor was used almost half of the patients had psychotic symptoms (20, 21), the return of specific hallucinations and delusions that some patients had shown years before has been reported (21).

CASE HISTORY

The first patient, 24-year-old, unmarried, female, was admitted to the university hospital after she had attempted suicide by jumping out of a window at the command of her auditory hallucinations. As a result she had broken a leg, which made an operation under general anaesthesia necessary. Afterwards she seemed confused: psychiatric examination showed that she was still suffering from auditive (imperative) and also from multi-coloured visual hallucinations (in the form of 'ghosts'). She stated that time was going very fast, was 'bombing her', or had come to a complete standstill. Movements were so fast that she was unable to follow them. The white hospital room seemed larger and full of colours and in combination with the 'ghosts' it resembled a temple. Faces of doctors and nurses were impossible to recognize as a result of deformation and colouring.

She was often extremely perplexed and complained about strange bodily feelings and sometimes haptic hallucinations. Anxiety was overwhelming, though she remained passive most of the time.

Occasionally this akinetic state was disrupted with the risk of violent suicide. Voices ordered her to burn or otherwise mutilate herself. Wide pupils, perspiration, tachycardia etc., even when she was not anxious, indicated a strong orthosympathic involvement.

This state, resembling that described for experimental psychoses induced by hallucinogenic chemicals like LSD, mescaline etc. was not affected by neuroleptics.

During the two months following admission, neurological symptoms became prominent: signs of neuropathy, diplopia and progressive paresis. Vitamin B_{12} was given in large doses: the neurological symptoms disappeared within a few days. The hallucinations gradually disappeared, but accidentally a Dolviran^{R} tablet was administered, containing a.o. barbiturates. Within an hour the hallucinosis described before, fully re-appeared. An acute intermittent porphyria (AIP) was strongly suspected then.

Cataleptic states, lasting several hours and sometimes preceded by abdominal cramps completed the picture. Once an epileptic fit occurred. Fatal outcome was feared when Cheyne-Stokes breathing patterns were observed.

On the assumption that our patient was suffering from AIP a diet, rich in carbohydrates, free of fat and with minimal protein (especially with a low content of the aminoacids methionine, serine, glycine and tryptophan) was given, when necessary, by force. To the surprise of everyone the patient recovered completely within four days and no residual symptoms could be demonstrated.

Short relapses occurred after the (forbidden) eating of herrings and later of French fried patatoes with mayonaise, and often in the premenstrual period.
For a period of four months our patient remained free of psychotic symptoms. But during a premenstrual period she suffered from a dysforic mood and thereupon refused to take any food. During the following weeks a totally different clinical picture developed. She showed a strong tendency to sing all day long, to make repetitive compulsive movements; she walked excitedly along the corridors and did not sleep or eat. There were no hallucinations but patient showed clear paranoid delusions. Instead of the akinetic-hallucinatory mescaline or LSD-like syndrome a hyperkinetic-paranoid amphetamine-like syndrome had developed and in concordance with the latter, neuroleptics were able to suppress the symptoms.
Adding extra tryptophan (1.5 gram/day) to the diet, made the akinetic-hallucinatory syndrome re-appear. After high calorie feeding for a few days she improved.
Further premenstrual induction of (pre)psychotic symptoms was succesfully prevented by regular medrogeston (Colpro®) intake.

Previous psychotic episodes

From descriptions of previous clinical admissions the great diversity of psychotic states was striking. Not only regarding the different pictures reported, but also with regard to the length of the psychotic episodes, varying from days to months, although complete recovery after every episode was evident.
Extreme states of depersonalization, especially of the somatopsychic type, during which patient said to feel like a robot, walking on fluff etc. were reported. These feelings of depersonalization were often followed by auditory hallucinations such as the singing of birds and voices commanding her to commit suicide.
Also short perceptual distortions of faces and hallucinations of coloured stains and circles were reported. Often her experiences were extremely terrifying - auditory and visual hallucinations of yelping wolves, roaring lions and deformed human faces and bodies.
Hypomanic periods, especially during evenings and nights, besides prolonged depressive episodes with distinct feelings of insufficiency and worthlessness were frequently reported but often these symptoms were dominated by paranoid ideation.

Diagnoses of temporal lobe epilepsy and manic-depressive illness were consid-

ered. Electro-encephalography did not substantiate the idea of temporal lobe epilepsy. Carbamazepine treatment had no effect and moreover seemed to worsen the psychosis. Treatment with lithium did not prove to be effective. Neuroleptics had some beneficial effects when sedation occurred. Recovery seemed to occur spontaneously and behaviour between psychotic episodes is described as 'impressively' normal.

Laboratory findings

Renal and liver function tests, red and white blood cell count, and hematogram were normal. Vitamin deficiences of folic acid, B_{12} (estimated before the vitamin B_{12} administration), B_1 and B_6 could not be demonstrated.
Also urinary corticosteroid excretion and thyroid function were normal.
Concentrations of uro- and coproporphyrines in urine and copro-and proto-porphyrines in faeces were repeatedly normal. After the Dolviran® tablet had accidentally been administered porphobilinogen (PBG) was qualitatively present in urine. Uroporphyrin I-synthetase concentration in red blood cells was also normal.
During psychotic states the glycine concentration in urine was increased.
Electro-encephalographic recordings, made during psychoses, did not show distinct anomalies.

PSYCHOTIC ILLNESS DUE TO ACUTE INTERMITTENT PORPHYRIA ?

In the present case history three aspects deserve attention: firstly, the frequent psychotic episodes since the menarche showed a great diversity of symptoms, whereas recovery was always complete.
Secondly, the clinical picture as observed after operation, resembled the hallucinogenic drug-induced state of LSD and mescaline. A later episode bears all the characteristics of an amphetamine-like psychosis.
Thirdly, the clinical course, the induction of the psychoses and concomitant somatic manifestations and the beneficial effect of the glucose diet led us to consider the diagnosis of acute intermittent porphyria as the basic metabolic disturbance.
However, the assumption that the underlying basis of the psychoses of our patient was porphyria, could not be confirmed biochemically.

Shortly after the successful treatment of the first patient, another girl was admitted into the university hospital, who was also suffering from a psychosis

characterized by multiple disturbances of sensory perception and catatonic features, acutely evoked after administration of barbiturates and sulfapreparations. Abnormal porphyrin excretion was found in urine. Together with the observations mentioned above, this aroused our interest in the psychiatric aspects and the biochemical basis of porphyria.

Psychiatric aspects of acute intermittent porphyria

AIP with its high incidence of mental symptoms is an attractive model for studying the molecular bases of psychiatric diseases (22).
Psychiatric symptoms often accompany attacks of the hepatic porphyrias, especially acute intermittent porphyria, porphyria variegata and hereditary coproporphyria.
The incidence of psychiatric symptoms assumed to be related to the porphyric disease is 15-80% (23, 24, 25). Psychiatric symptoms can precede the neurological and abdominal manifestations of porphyric attacks, or may be so overwhelming that little attention is paid to them (26, 27). In this respect our first patient was no exception.
These psychopathological symptoms are not found in porphyria cutanea tarda (symptomatica) (PCT), or, when present, they are related to the etiology of PCT, such as alcohol addiction, intoxication by herbicides, pellagra, etc., and are not the consequence of the increased porphyrin biosynthesis (23).

According to the literature five types of psychiatric syndromes can be distinguished during porphyric attacks.

a) anxiety and emotional lability (28, 29).
b) so-called hysterical behaviour such as 'loud shrieking and a curious position in bed, rarely noted in other somatic diseases' (30). This behaviour seems to be induced by colicky pains, which in its turn is often misdiagnosed as a symptom of hysterical conversion, in particular when curious pareses are observed (31, 32).
c) confused or delirious states, clearly pointing to an organic brain syndrome (23, 24, 28, 29, 30, 31). When hallucinations are present they are mostly of a visual nature (33).
d) depressed, dysphoric or apathic states of mind, in some cases not subsiding immediately after an acute attack (24, 32).
e) 'schizophrenic' states (the term is loosely used for all sorts of psychoses with unimpaired consciousness) (34, 35).

It remains obscure, however, whether these schizophrenias and porphyric diseases are pathogenetically related, or whether both clinical conditions occur in a patient by chance. Some authors suggest a possible causal relationship, but this is refuted by others (29, 36).
An exception in this respect is the report of a prolonged auditory hallucinosis which was found to be related to AIP (37).
Thus, it is evident that with regard to the types of mental disturbances mentioned in the literature, our first patients, who were supposed to suffer from porphyria, are great exceptions. Their characteristically psychotic states without impaired consciousness, not resembling the classical organic brain syndromes have not been reported previously.

Biochemical aspects of porphyria

Before us, many authors have tried to understand psychiatric symptomatology in porphyric disease from what is known of the deranged biochemistry of the latter. Porphyrins are synthesized from succinate and glycine via the enzyme aminolaevulinic acid synthetase. ALA synthetase is the rate-limiting step in the porphyrin biosynthesis and this enzyme can be activated by steroids or barbiturates and can be inhibited by glucose and by the end product heme (23).
A deficient enzyme in the porphyrin pathway (uroporphyrin I-synthetase in the case of AIP) will cause a decreased production of heme. This leads to a decreased feedback repression and activation of ALA synthetase thus increasing the formation of precursors of the porphyrins (ALA and PBG). During induction of ALA synthetase more succinate and more glycine will be needed.

Similar to the hypothesis to be forwarded in this thesis is the idea of De Matteis (38). De Matteis reasoned that the preferential metabolism of glycine through the succinate-aminolevulinic acid cycle rather than the acetate-aminoaceton cycle arises from decreased availability of acetyl CoA. This will also result in a decreased synthesis of acetylcholine in nervous tissue.
When compared to pharmacologically induced anti-cholinergic states, such a hypothesis can explain the occurrence of confused and delirious states. It is partly contradicted, however, by the fact that normal quantities of aminoaceton are excreted in AIP (39).

Most theories focus on the products of the aberrant porphyrin synthesis to explain the observed neuro-psychiatric disturbances in porphyric diseases.

During an attack of AIP aminolevulinic acid and porphobilinogen are synthesized and excreted in abundance due to the failing endproduct (heme) inhibition of the enzyme ALA synthase. These products may be responsible for psychiatric symptoms, although ALA and PBG hardly penetrate into the central nervous system (CNS) (approximately 4% of the blood concentration is found in liquor). But when administered intraventricular in animals it does give behavioural changes (40).

In addition, it has been demonstrated that both ALA and PBG have a depressant effect, like gamma aminobutyric acid (GABA) on the spinal cord, ALA more so than PBG. The ALA concentration needed for this effect is equal to the blood concentration attained during an acute attack of AIP (41).

More investigators have pointed out the effects of ALA on the GABA-ergic neurons (42, 43, 44), and recently Brennan and Cantrill (45) showed that ALA can compete with GABA for presynaptic receptors in the mammalian CNS. It reduces potassium depolarization-induced release of GABA in a concentration ($1.6\text{-}2 \times 10^{-5}$ M) that can be reached in cerebrospinal fluid during an acute attack of AIP. This effect is of special interest, as it may offer an explanation for the occurrence of hyperexitability and seizures observed during acute attacks of porphyria. It is unlikely that the characteristic psychoses presented here can be understood from such a disturbance of the GABA-ergic system.

The organic brain syndromes, confused and delirious states, observed during an attack of AIP, can also be caused by hyponatriaemia, which is often the result of excessive vomiting, renal loss of sodium or inappropriate secretion of anti-diuretic hormone (46).

Mauve factor

Another possibility that relates porphyria and its concomitant psychoses was the finding of an Ehrlich-positive substance, thought to be related to the pyrroles. This substance was reported to be found in the urines of schizophrenic patients (mainly paranoid and undifferentiated types; 47).

This mauve factor, named after its colour in the chromatogram, led Hoffer and Osmond, a little prematurely, to introduce a new entity of psychiatric disease, Malvaria (48).

Patients who excreted the mauve factor, thus suffering from Malvaria, were reported to be severely psychotic, with perceptual changes, thinking disorders, incongruencies in affect and behaviour. The mauve factor has been demonstrated by several groups of investigators, and, although most frequent (about 50%)

found in urine of schizophrenic patients, it was also present in urine of healthy persons, cancer patients, epileptics, alcoholics, neurotics and otherwise mentally disabled patients (49, 50, 51).
Finally, the mauve factor in urine of schizophrenics was identified with phenothiazine metabolites, a fact that might be due to a different extraction method (53).
Nevertheless, the Irvine and the Sohler group succeeded in identifying the mauve spot as being 2,4-dimethyl-3-ethyl pyrrole (kryptopyrrol) which interestingly resembles the indol tryptamine and related hallucinogenic substances (53, 54).
Gendler et al. failed, however, to detect kryptopyrrole or its isomer haemopyrrole in schizophrenics and controls (which includes AIP patients) (55).
With refined methods the 'natural' kryptopyrrole was proven to be identical with the oxidized lactam form of heamopyrrole (2,3-dimethyl-4-ethylpyrrole): viz. hydroxyheamopyrrollin-2-one (OH-HPL).
This metabolite is supposed to be easily formed from PBG and was found in the urines of patients with AIP and of psychiatric patients (56). This OH-HPL was found to be related to the urinary ALA concentration in AIP and was also increased in 4 out of 7 schizophrenic and 4 out of 6 patients suffering from organic brain syndromes. In these psychiatric patients no relation with ALA (or PBG) concentration has been found (57).
Gorchein reports that OH-HPL could not only be detected in the urines of schizophrenics, but also in those of normals of otherwise general medical subjects. The excretion of these monopyrroles in AIP did not correlate with ALA of PBG concentration or the clinical state of the patient (58).

In conclusion, the relation of the monopyrroles to psychoses and porphyria remains conflicting and obscure at this moment. Nor do the other findings and theories regarding the relationship of porphyria and psychoses offer an explanation as to how porphyric disease and hallucinogenic-like psychotic states can be related.

EXCESSIVE PYRROL SYNTHESIS, ONE-CARBON METABOLISM AND BIOGENESIS OF HALLUCINOGENIC SUBSTANCES: A HYPOTHESIS

The assumption of the theory presented here is that in the patients studied, hallucinogenic substances were endogenously synthesized due to aberrant pyrrol synthesis.
The idea of endogenous formation of hallucinogenic substances has recently been

reviewed by Bruinvels (59). From the data presented in the literature it was concluded that psychotomimetic substances could be synthesized endogenously from the normal monoamines under conditions in which methylene and/or methyl tetrahydrofolic acid (THF)concentrations are increased to such an extent, that the normal flow of one-carbon units via the vitamin B_{12}-dependent enzyme homocysteine methyltransferase (yielding methionine) becomes impaired. One-carbon groups are thus trapped.
Under such circumstances abnormal methylation of monoamines may become possible.
Many of these products are identical with well-known potent hallucinogens, a fact that has led to much research and speculations about this theory of abnormal methylation next to other theories in the area of schizophrenia (60, 61, 62, 63).
Later it was shown that it is not methylation but cyclization of monoamines by a non-enzymatic reaction of formaldehyde derived from methylene-THF that is probably responsible for the formation of psychotogenic substances (For a review see: 64).
This induced the hypothesis that 'hyperformaldehydism' may be the biochemical etiology of schizophrenia (65).

On realizing that an excess synthesis of methylenated folates could be the key problem, we sought for a biochemical explanation of the case presented.
As pointed out by Bruinvels (59), the ultimate source of one-carbon neogenesis is the hydroxymethyl group of serine.
This aminoacid is converted into glycine by the enzyme serine hydroxymethyl-transferase (SHMT) in which tetrahydrofolic acid, as a co-factor, accepts the one-carbon moiety as methylene (CH_2=THF). The enzyme requires pyridoxal 5'-phosphate for activity (66, 67, 68). Subsequently, assuming that the patient described was suffering from AIP, we realized that great amounts of glycine had to be formed from serine in order to meet the increased demands for glycine during increased pyrrol synthesis in porphyric attacks. Glycine and succinyl-CoA are the precursors in pyrrol synthesis. Thus, during excess pyrrol synthesis abundant formation of CH_2=THF will occur, since exogenous sources of glycine are even in normal circumstancs insufficient to meet the daily needs (67).

METHYL(ENE) TRAPPING AND PSYCHOSES DUE TO OTHER METABOLIC DISEASES

Previously, the idea of trapping of one-carbon units and synthesis of hallucinogenics was studied or at least mentioned as a possible cause of psychotic states in relation to well-known disturbances in metabolism and transfer of active one-carbon groups. Thus, it is worthwhile to look into these metabolic disorders and study possible links with the present case. The hampered one-carbon transfer may be caused by vitamin B_{12} deficiency or genetic of functional deficiencies of the enzymes involved in the transport, in particular CH_2=THF reductase, CH_3-THF homocysteine methyltransferase, methionine adenosyl transferase, and cystathionine- beta-synthetase.

A rise in plasma folate (which is mainly CH_3 -THF) is observed in B_{12} deficient animals, while the intracellular fraction of polyglutamate folates decreases and the pool sizes of monoglutamate remains constant.
The ratio of methylated polyglutamate products versus non-methylated products is increased, while the amount of CH_3 -THF is constant (69). Smith et al. also showed that with vitamin B_{12} deficiency the folate content of liver decreases including the methylated fraction, and pointed to the fact that plasma folate content is less than 1% of that in liver (70).
In agreement with the latter reports are findings demonstrating that folate metabolism fails (71) and the oxidation of histidine, formate, sarcosine, serine and glycine is decreased (72).
It is concluded that in a vitamin B_{12} deficiency the uptake and possibly the retention of folates is afflicted, thus interfering with the simple idea of methyl trapping.
In agreement with these animals data, the clinical literature is also disappointing is this respect: the type of psychosis that may be expected as the result of methyl trapping, viz. a hallucinogenic drug - like psychosis has not been unequivocally reported.

Nevertheless, mental symptoms ascribed to vitamin B_{12} deficiency are estimated to be present in 4-16% of patients suffering from such a deficiency (73).

From the introduction, during the fifties, of routine serum vitamin B_{12} assays in clinical practice (74), many reports have been published that pointed to the emergence of mental symptoms a long time (up till years) before anaemic or

neurological symptoms were observed; or mental symptoms that had been minimal and hence (had) escaped attention (75).

The reported cases of (pre)'megaloblastic madness' (76) vary widely in respect to their symptomatology: from neurasthenic complaints (especially fatigue) to apathy, from confusional to delirious states, from memory impairment to gross dementia, from regressive behaviour to stupurous states with incontinence etc. are described.
However, severe retarded depressions with a tendency to paranoid ideations or delusions and occasionally a (hypo)manic state are also mentioned (73 - 80).
In many cases favourable outcome of B_{12} therapy is stressed, which also occurred in the case of a 35 year-old male patient who, 9 years after gastrectomy, had developed a serious organic psychosis. Treatment with B_{12} injections, despite normal serum B_{12} concentration, resulted in a prompt and dramatic complete amelioration (81).
(This patient and the patient presented here both demonstrate the necessity of discriminative assays for methylated and non-methylated B_{12}, since oversaturation of the B_{12} pool with methylgroups will result in reduced availability and functional deficiency of the non-methylated B_{12} fraction, while nowadays estimations of serum B_{12} comprises methylated as well as non-methylated B_{12}).

Surveys of general psychiatric populations, including patients with functional psychoses, often show high incidences, up till 10%, of low serum B_{12} levels with or without low folate concentrations. Pernicious anaemia has only incidentally been found as the cause of the deficient state.
Poor feeding habits and deficient, vegetarian diets, in (arterio sclerotic) demented patients in particular are held responsible (82, 83, 84).
It appears that there is no causal relationship of the deficient B_{12} state with the functional psychoses, though precipitation of affective illness remains a theoretical possibility.

A causal relation between B_{12} deficiency and depression (and mania) is further refuted by a prospective study of Shulman (85). Significantly more depressions were found to be correlated with vitamin B_{12} deficiency.
However, the causal relation is unlikely in view of the high incidence of depressions among relatives and previous episodes of depressions in the index patients. Moreover, relapses of depression during vitamin B_{12} therapy were observed.

A careful study of Shorvon (74) showed that in isolated vitamin B_{12} deficiency states with concomitant megaloblastic bone marrow 20% of the 50 patients suffered from (depressive) affective symptoms and 26% had organic features. In contrast, 56% of the 34 patients with a solitary folate deficiency, had affective disturbances and 27% organic complications. Thus, in this study vitamin B_{12} deficiency was less frequently associated with affective disturbances than folate deficiencies.
Apparently functional florid psychotic states are not caused by vitamin B_{12} deficiencies.
The mention of a 'schizo-affective reaction' related to a low normal B_{12} concentration (155 pg/ml) (86) cannot be considered to be proof of the contrary.

Phenytoin and psychoses

Another clinical situation that might disturb methyl transfer is during anti-convulsive treatment of epilepsy. Many anticonvulsants have been implicated in folate deficiency eventually resulting in megaloblastic anaemia. Evidence has been presented that phenytoin interferes with the conversion of folic acid to CH_3-THF outside the CNS (87, 88) and may therefore be of special interest.
This fact explains the frequently reported low folate levels during phenytoin treatment, since methylated THF makes up the largest pool of plasma folates and in daily practice this fraction is measured by a microbiological assay (L. casei). CSF folate concentration will also be afflicted since CH_3-THF is the only folate derivative that is actively transported by the blood-brain-barrier into cerebrospinal fluid (CSF) up to three times the plasma concentration (89, 90, 91). Diphenylhydantoin lowers CSF folate most (92).
In the study of Mattson et al. (87) a rise in CSF folates in drug induced folate deficient patients is observed after 'Leucovorin' (= 5-formylTHF), but not after folic acid therapy.
In addition, Krause et al. (88) showed that serum and CSF concentration of unreduced folates, as measured by a special competitive protein binding assay, were similar in hydantion treated epileptics and controls.
It may be concluded that the transfer of active C fragments in these patients is unimpaired. However, the reduction of folic acid to THF is decreased and the capacity to bind one carbon units reduced, leading to a paucity of methylating processes in the body.

In the light of these findings the widely cited report of Reynolds of schizo-

phrenia-like psychoses during anticonvulsive treatment is of considerable interest (93). In four patients, all suffering from temporal lobe epilepsy, the development of unmistakably florid schizophreniform psychoses (without dysperceptions) was observed after these patients had been treated with a combination of phenobarbitone and phenytoin most of the time. Recovery from psychosis resulted after folic acid and vitamin B_{12} administration. In one patient this was the only treatment. Next to a low folate level, a rather low B_{12} serum concentration (180 pg/ml) was also found in 3 patients during anticonvulsive therapy. It is presumed that the latter disturbance is secondary to the antifolate action of the anti-epileptic drugs (94).

Here also, the exact quantitative relation of methylated versus non-methylated vitamins will considerable add to the understanding of the reported phenomena.

Reynolds relates his findings to the transmethylation hypothesis of schizophrenia (93). However, in the light of present limited knowledge of phenytoin treatment and folate metabolism this seems hardly tenable. Following parallel lines of reasoning Levi and Waxman (95) postulated that 'schizophrenia' is not provoked by excessive and faulty methylation of monoamines, but is instead due to a decreased methylation capacity of these patients. A deficiency or functional limitation of the enzyme methionine adenosyl-transferase or its co-factors is suggested as a possible cause of schizophrenia.

Decreased activity of S-adenosylmethionine (SAM) dependent methylation, however, could not be demonstrated in brains of schizophrenics at autopsy (96), and in addition, the activity of methionine adenosyl-transferase in erythrocytes has also been found to be normal in schizophrenic patients (97). In contrast, an uncontrolled (for diet, environment and therapy) study of Carl et al. (98) showed a significant lower activity of serine hydroxymethyl transferase (SHMT) and methionine adenosyl transferase in blood cells of schizophrenics compared to normals.

Folate deficiencies and psychosis

As was to be expected a folate deficiency alone has not been demonstrated to be causally related to florid psychotic states. Depressions, fatigue states, organic brain syndromes, and neurological symptoms are described in folate deficiencies (99, 100, 101). A folate deficiency may affect neurotransmitter metabolism, since the pteridines and possibly the pteridine part of the folate molecule are important as a co-factor for tyrosine, phenylalanine, and tryptophan hydroxylase activity (102), which may explain the depressive symptoms.

Methylene reductase deficiency

A genetic deficiency of the enzyme methylene reductase has been demonstrated in children with severe mental retardation and a wide spectrum of neurological findings associated with low folate levels, homocystinuria and moderate homocystinaemia, normal of low plasma methionine levels and without abnormal hematological findings (103, 104, 105).

Freeman et al. (106) reported a mildly retarded adolescent girl lacking the classical clinical manifestations of homocystinuria but having concentration difficulties after the menarche. Her IQ was 60. After an episode with severe abdominal pains at the age of 14, she lost contact with her surroundings, perseverating and giggling inappropriately. Her verbal IQ was 46, further psychological testing was 'indicative of a schizophrenic reaction'. Despite continued neuroleptic treatment a psychotic episode emerged with visual and auditory hallucinations, nightly terrors, and feelings of being persecuted. The episode was further characterized by drowsiness, falling asleep, muteness, and incoherent mumbling. There was a questionable seizure, she was incontinent and had to be fed.

Nitrofurantoin medication for a urinary tract infection evoked a rapidly progressive peripheral neuropathy. Folic acid (20 mg/day), administered for 14 days, resulted in improvement of the psychotic state and intellectual function. In later psychotic periods, the authors mention Babinksi responses, superimposed on the neuropathy, a slow diffusion in the electro-encephalogram, disorientation, and inability to recall name and birth date. Recovery from these episodes occurred after folic acid administration.

One full sister with an IQ of 62 performed well and showed no psychotic symptoms. Neither did she show anomalies of the lens, osteoporosis or thromboembolic phenomena which are present in cases of homocystinuria due to a cystathionine beta-synthetase deficiency. In both sisters a reduced activity of the 5,10-methylene tetrahydrofolate reductase activity was demonstrated.

The psychoses, on the strength of psychological tests (Bender-Gestalt and Rorschach) and the opinions of several psychiatric consultants, were labelled as (catatonic) schizophrenia, although the authors in their discussion and by putting the word 'schizophrenia' in the title in quotation markts, apparently leave room for another diagnostic view.

The report of this case history and biochemical findings led to further speculations on and research for a decreased reductase enzyme activity in schizophrenic psychosis. However, there is no solid evidence that the enzyme is deficient in

schizophrenia (107).
Apart from biochemical studies and speculations there is little reason to characterize the psychotic illness of Freeman's patient as schizophrenic.
When the IQ has dropped to 46, Bender-Gestalt and Rorschach tests cannot be used to substantiate the diagnosis schizophrenia. The drowsiness, the incoherent mumbling, the muteness, the incontinence, the disorientation reported later on, even when possible seizures are not taken into account, the electro-encephalographic and other neurologic complications, favour the diagnosis of an organic mental syndrome characterized by florid symptomatology. The title of Freeman's article is rather misleading and may be illustrative of the vague way the term 'schizophrenia' can be used in America.

Methyl transferase deficiency

A case of homocystinuria and psychosis due to a deficiency of the CH_3-THF homocysteine methyl transferase has been reported (108). A 14 year old boy suffered from an 'acute psychosis'. He was also moderately mentally retarded (IQ 50 WIS for children) and showed some neurological disturbances. Spontaneous recovery from the psychosis was observed. Very young children have been reported to be more seriously mentally, somatically and biochemically disturbed (103, 109).
The inability to metabolize vitamin B_{12} adequately has also been demonstrated in severely ill new-born infants (110, 111, 112). These studies do not provide further insight into the pathogenesis of the psychosis in our patient.

Cystathionine beta-synthetase deficiency

A deficiency of this enzyme is the most frequent cause of homocystinuria (109). The presence of psychosis or schizophrenia in families with homocystinuria has been reported. In one patient with homocystinuria possible schizophrenic symptoms were present and it was hypothesized that the abundance of methyl groups in the form of methionine in this disorder, caused the psychotic illness, a view that is concordant with the idea behind the methionine loading tests (113).
The psychoses subsequently reported, however, are clearly variable organic brain syndromes (114-117), and the 'schizophrenia' of the relatives are probably not related to the homocystinuria, being the chance occurrence of both conditions in one family (118, 109).
Homocystinuria has not been found in retrospective analysis of patients with

schizophrenic psychoses (118).

Thus, the clinical pictures presented in the literature do not support unequivocally the idea of methyl(ene) trapping causing LSD or mescaline-like psychoses by the known enzyme and/or co-factor deficiences in the methyl transfer pathway.

Conclusion

In addition to the knowledge that clinical practice gives poor substantiation to the idea of methyl trapping and concomitant characteristic psychiatric disturbances, it is equally important to realize that it is a matter of doubt whether the enzyme deficiencies mentioned above indeed cause methyl(ene) trapping to such extent that abnormal one-carbon transfer will occur.
The normally operative regulatory mechanisms of the methyl metabolism would tend to prevent such a metabolic aberration.
Though these regulations are not yet completely understood or investigated there is ample evidence that the different enzymes involved in one-carbon transfer can be inhibited by feedback mechanisms and thus prevent excessive accumulation.

Some of these mechanisms have been elucidated in mammalian tissues (119-122) and are briefly discussed here:
Serine hydroxymethyl transferase (SHMT) is inhibited by one of the derivatives of CH_2=THF, namely 5-formyl THF.
CH_2=THF itself and also its derivatives 5,10-methenyl THF, 10-formyl THF and 5-formyl THF inhibit the reduction of dihydrofolate to THF, resulting in a slow reduction of stored THF (most of it being the polyglutamate form of CH_3-THF).
CH_2=THF is normally irreversibly reduced to CH_3-THF and this latter product strongly inhibits SHMT.

$$\underset{\text{formyl}}{-CHO} \xleftrightarrow{\text{cyclohydrolase}} \underset{\text{methenyl}}{\equiv CH} \xleftrightarrow{\text{dehydrogenase}} \underset{\text{methylene}}{=CH_2} \xrightarrow{\text{reductase}} \underset{\text{methyl}}{-CH_3}$$

The end product of methyl biogenesis S-adenosyl methionine (SAM) inhibits in turn the methylene-reductase, while its demethylated product S-adenosyl homocysteine stimulates the reductase.
Such a cascade of inhibitory mechanisms enables an accurate tuning of one-carbon metabolism in many circumstances; trapping at one place will cause

inhibition of preceding metabolic conversion and transfer of one-carbon groups. Moreover, the serine - glycine conversion by SHMT is completely reversible, glycine can react with CH_2=THF to reform serine (67). Although the equilibrium is slightly in favour of glycine synthesis, abundant production of glycine and CH_2=THF is not likely to occur under normal circumstances (see also serine - glycine metabolism).
Therefor we can agree with Tisman et al. that 'the methylfolate-trap hypothesis should be put to rest, since data from many laboratories cannot be forced to fit such a hypothesis' (123).
Though the comment of Tisman et al. applies to vitamine B_{12} deficiency alone, we would like to extend it to any disturbing factor along the one-carbon pathway from serine to SAM.

Only conditions under which the normal inhibitory regulatory actions of the methyl biogenesis can be circumvented, will result in an increased synthesis and quantitively significant trapping of one-carbon moieties.

Increased serine to glycine conversion during enhanced pyrrol synthesis may be such an event in which the body as a side-effect of its demand for glycine is forced to produce and accept more one-carbon units than are needed for its methylation processes. Of course, other metabolic situations may also cause such an unwanted accumulation of active one-carbon fragments.

SERINE - GLYCINE METABOLISM

The daily rate of glycine synthesis is approximately 1 gram/kg body wt, the endogenous synthesis of glycine is 10-50 times the normal dietary supply. Collagen contains 30% glycine, while 60% of non-collagen protein is made up of glycine (67). Most glycine is needed for creatine syntheses and is made almost exclusively via the hydroxy-pyruvate - serine pathway (67, 124).
The other important function of serine-glycine metabolism is the biogenesis of one-carbon units. The end product, S-adenosyl-methionine (SAM), is the predominant methyl donor in almost all methylation processes and is regarded also to be the most important substance in the regulation of the de novo biogenesis of one-carbon groups by its feedback inhibition of methylene reductase, enabling a rapid regulation of methyl biogenesis (see below).
The quantitatively most important acceptor of methyl groups (via SAM) is the creatine synthesis. In normal, non-fasting conditions some methyl neogenesis is

needed, but most methyl groups are derived from the methyl donors choline and methionine by food intake (124).
According to Mudd and Poole (124), homocysteine recycling doubles under conditions of limited protein intake. Thus, during limited protein intake or starvation, the body is completely dependent on the serine-glycine conversion for its creatine and methyl synthesis.
Arnstein and Neuberger (66) also found that serine is the methyl donor in these circumstances. Glycine itself was found to be insufficient.
It is easily understood that the activity of the glycine cleavage enzyme - breaking down glycine to NH_3 and CO_2 and yielding also active one-carbon groups in the form of CH_2=THF - is very low under normal conditions in mammalian species (125), since glycine is an important aminoacid that is utilized in many ways, e.g. in addition to the synthesis of creatine, synthesis of purines, pyrrols, and the conjugation of bile acids etc.
Glycine catabolism through the succinate-glycine or amino-aceton cycle is quantitatively unimportant (125).
The activity of the enzyme serine dehydratase in the human metabolism, in contrast with that of the rat, remains obscure, but it may play some role in gluconeogenesis during prolonged starvation (125), when body proteins (up to 100 gr/day) are broken down in order to supply the glucose dependent energy needs of the brain (126).
In normal, non-fasting conditions, the serine-glycine equilibrium is in favour of glycine synthesis (67).
When administered, glycine is also rapidly converted to serine. In addition, there is evidence that glycine methylation serves for metabolic removal of 'excess' labile methyl groups (127).
The complex and poorly understood serine-glycine metabolism is further complicated by cellular compartimentization (67, 121, 125, 128-131). From several animal experiments it can be concluded that serine and glycine are synthesized in the cytosol, but serine is actively transported into the mitochondria, where the serine concentration is responsible for glycine formation. In contrast to SHMT the cleavage enzyme complex is confined to the mitochondria; the two iso-enzymes of SHMT are not identical. Methylated folates diffuse passively across membranes.

It can be concluded that the complexity of the serine-glycine metabolism offers many possibilities for derangement. Increased pyrrol synthesis, abnormal activity of the succinate-glycine cycle, the amino-aceton cycle, the glycine cleavage

enzyme, disturbances in active transport of serine and/or (iso)enzymic changes can all be held responsible for upsetting the normal regulations of the serine-glycine balance.
But at least it is not inconceivable that acute porphyric attacks and starvation as well may be powerful stimuli for increased serine to glycine conversion, which is interesting in the light of the beneficial effect of the serine-glycine deficient, calorie-rich diet on the psychosis of our patient.

PRELIMINARY HYPOTHESIS

As stated before, any event that will lead to (temporarily) excessive formation and piling up of methylenelated folates may induce the formation of formaldehyde and hence cyclization of monoamines.
So whatever the cause, abnormal increased expenditure of glycine which entails demethylation of serine, has to be responsible for the psychotic attacks.
It was argued that in our patient the basic metabolic disturbance is latent during 'normal' episodes, but that an appropriate induction will stimulate serine to glycine conversion to such a measure that methylene trapping will occur.
Therefore, the assumed abnormal catabolism of serine and glycine might be demonstrated even during normal episodes after loading the patient with serine or glycine; plasma serine and glycine concentrations after loading might be different when compared to control loadings.
Distinct psychopathological changes identical with those previously experienced by the patient during the psychoses, emerged after a low oral dose of aminoacid (2 mmol/kg body wt.), thus suggesting that this was a suitable line for further study.

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CHAPTER II.

SCHIZOPHRENIA-LIKE PSYCHOSIS CAUSED BY A METABOLIC DISORDER *

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Introduction

Metabolic diseases are often accompanied by psychiatric symptoms-e.g., Wilson's disease (1), Hartnup's disease (2), and porphyria (3). We observed some patients with a characteristic psychosis which bore a striking resemblance to a drug-induced psychosis of the mescaline type. These patients were suspected of having a porphyric disease, and we wondered whether the metabolic dysfunctions occuring in porphyric diseases could be related to the psychosis.

In the porphyrias the increase in pyrrol synthesis demands increasing amounts of glycine; hence conversion of serine into glycine is accelerated and excess methyl groups are produced. The availability of excess methyl groups may result in faulty methylation of catecholamines (4).

On the basis of this working hypothesis we studied the serine and glycine excretion during and after psychosis and did loading tests with these aminoacids.

Subjects and methods

On admission all patients showed disturbances of affect, were depersonalised, and complained of perceptual distortions ('dysperceptions') of surroundings, colour, and time, and of other types of abnormal sensory perception apart from

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distinct hallucinations (5). None had impaired consciousness or disorders of thinking. They werd diagnosed as having schizophreniform psychotic syndromes.
Four female patients out of ten (3 male and 7 female) were further investigated because they did not improve with neuroleptic treatment.

Patient 1. - She was 24 years old, had had several admissions to psychiatric hospitals in the past seven years for symptoms which started after a surgical operation under general anaesthesia (including thiopentalsodium)-hallucinations, catalepsy, progressive polyneuropathy, and colicky pains.

Patient 2. - This 18-year-old patient had been admitted for an acute psychosis characterised by hallucinations and catatonic symptoms caused by medication with a sulphur preparation and barbiturates. She also had abdominal pain.

Patient 3. - She was 37 years old and premenstrual induction of symptoms was observed during each of her four admissions.

Patient 4. - The 27-year-old patient was very dysphoric and had intermittent hallucinations. Her symptoms, which included skin lesions, developed after she began taking contraceptive pills with a large oestrogen component.

Porphyrins were measured during and after psychosis in 24 h urine and in faeces (6), and aminoacid analysis was done on blood and 24 h urine (7).
The patients were given a diet rich in carbohydrates (405 g/day), moderately low in protein (62g/day), and very low in fat (19g/day), the approximate calorie intake being 2040 kcal/day.
The patients gave consent for a loading test in which serine or glycine (2 mmol/kg) was given 1 h before breakfast with yoghurt. This trial was done double blind after complete recovery from psychosis and with patients on the same diet as above. It was done while patients were in hospital and without any change in the normal daily routine. Behavioural scoring (see legend accompanying table) was done by nurses and two psychiatrists.
Four healthy controls, matched for age and weight, also underwent the loading test.
The committee on human experimentation of the University Hospital approved of these tests.

Results

Porphyria

Since the patients were suspected of having porphyria, a carbohydrate-rich diet, known to be of therapeutic value in porphyric disease (8), was prescribed. All

patients recovered from their psychosis within 2-5 days of taking this diet.
In patient 2 the raised faecal protoporphyrin excretion and the presence of porphobilinogen in urine on admission suggested porphyria variegata. In patient 4 the excretion of large amounts of urocarboxylic and heptacarboxylic porphyrin in the urine and isocoproporphyrin in the faeces suggested porphyria cutanea tarda. In patients 1 and 3 no abnormalities were found upon repeated analysis.

Aminoacids

The excretion of serine and glycine was measured in 24 h urine specimens along with that of alanine and tyrosine as reference aminoacids (see table).
During psychotic episodes serine excretion dropped in all patients. In addition patient 1 showed an increased excretion of glycine. The porphyric patients (2 and 4) had a more general disturbance of aminoacid excretion patterns. During remission none of the patients showed any abnormality in aminoacid excretion. Homocystinuria was excluded in all patients.

Loading Tests

All patients had psychopathological symptoms on serine loading (fig. 1). All became depersonalised, and three also had dysperceptions. In addition, patient 2 became very euphoric and had complex visual hallucinations. Patient 3 became very dysphoric, and patient 4 had simple visual hallucinations. The serine induced psychosis occurred about 5 h after ingestion of the aminoacid and lasted 3-6 h.
Glycine had no effect on three of the four patients.
According to the patients their experiences during the loading test were identical with those of their 'natural' psychosis.
None of the controls reacted to serine or glycine loading.

Discussion

The dysperceptions and the hallucinations were highly suggestive of drug-induced psychosis of the mescaline or lysergic-acid type. Since drug-induced psychosis was excluded, we thought that hallucinogenic substances could have been formed endogenously because of a metabolic dysfunction related to porphyria.
A theoretical relation between porphyria and psychotic behaviour is shown in fig. 2. During a porphyric attack the increased formation of porphyrins will demand larger amounts of the precursors glycine and succinyl-CoA (9). The increased demand of glycine can be met by demethylation of serine (10). During demethylation a methylene group is transferred from serine to tetrahydrofolic

EXCRETION OF SERINE AND GLYCINE

	Score*	No. of psychotic attacks	Serine	Glycine	Alanine	Tyrosine
Controls (n=4)	0	--	784±65	1685±233	444±172	123±15
Patients in remission (n=4)	0	--	788±74	1428±502	250±88	101±34
Patients during attacks						
Patient 3	2	3	211±6	1119±51	325±4	120±12
Patient 3	4	2	146(139;154)	698(781;616)	214(235;192)	91(86;96)
Patient 1	5	3	6±6	3382±805	346±117	104±29
Patient 4 **	5	1	30	52	50	40
Patient 2 **	6	1	111	592	81	18

* Scores: anxiety 1; dysphoria/euphoria 2; depersonalisation 3; dysperceptions 4; hallucinations 5; catatonia 6.

** Patients with porphyria.

Mean values given for control groups and for patients in remission; aminoacids values in micromol/1/24 h.

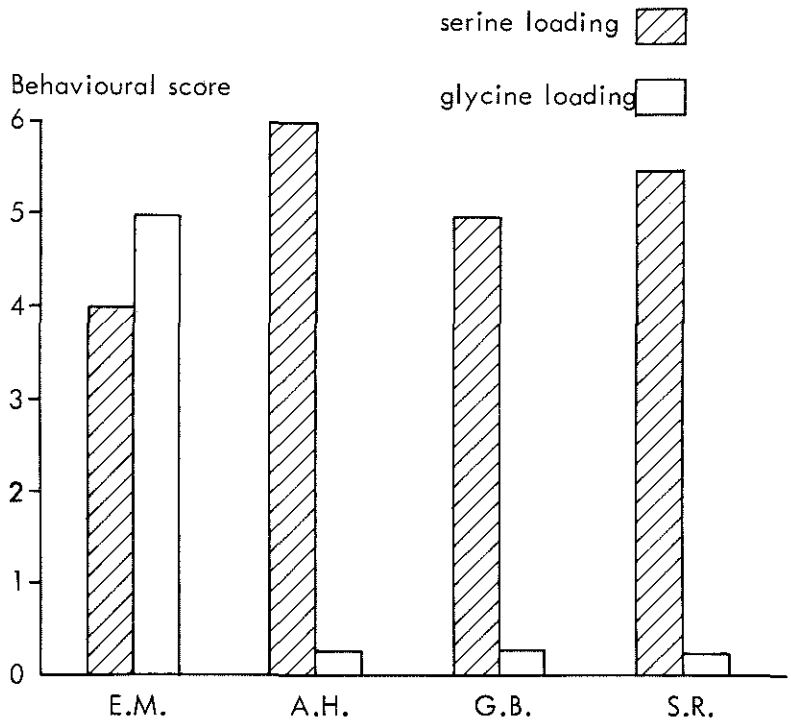

Fig. 1 - Behavioural score after serine and glycine load.
See footnote to table for scores.

acid (FH_4). The N^5, N^{10}-methylene tetrahydrofolic acid ($CH_2{=}FH_4$) thus formed is an active methylating agent, involved not only in normal methylation processes (via the vitamin B_{12}, homocysteine-methionine pathway) but also in possible abnormal methylation ($R_2H \longrightarrow R_2CH_3$) or cyclisation of monoamines (11-13) several of which are known to be psychotogenic substances (14).

The decreased secretion of serine in all patients during psychotic periods, suggesting increased comsumption of serine, indicated a central role for serine and glycine in this syndrome. More direct evidence for such a role was provided by the quick and dramatic effects of serine loading on all patients. However, since one patient also reacted to glycine loading, the simple hypothesis that increased conversion of serine into glycine is responsible for the psychosis will not suffice. Also, the relation with porphyria is not clear in all cases - a porphyric disease was proven biochemically in only two patients.

Further research in progress with patients having episodic psychosis characterised by dysperceptions shows that most of these patients react with (pre)

psychotic symptoms on glycine or serine loading, whereas patients with other forms of psychosis do not. Some disturbance of serine-glycine metabolism therefore seems to be involved in the schizophreniform psychotic syndrome described here.

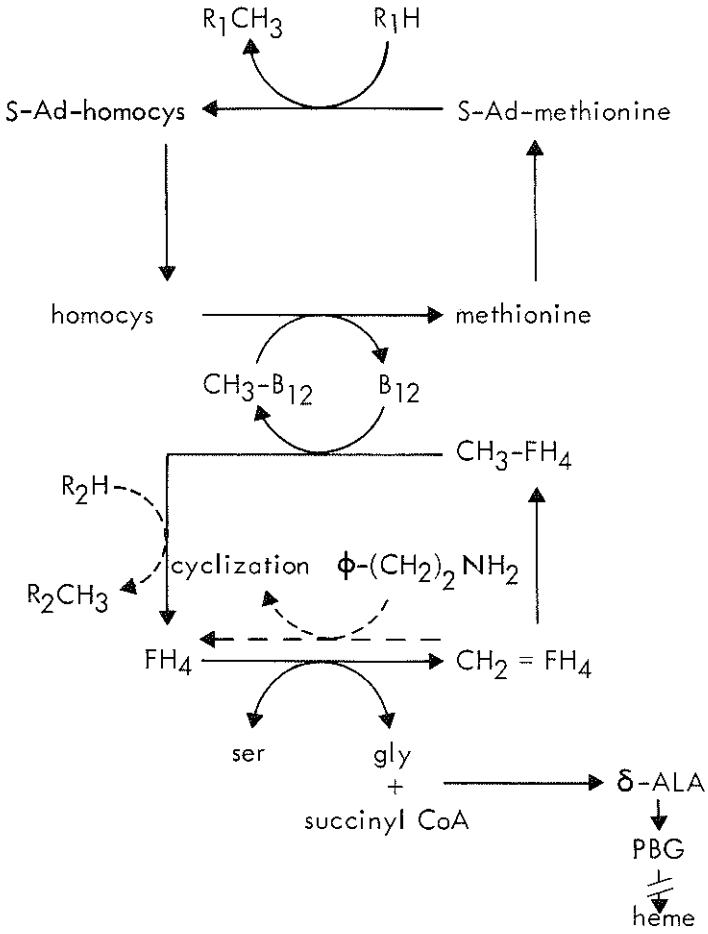

Fig. 2 - Porphyrin biosynthesis related to methylation processes.

Only the first part of the porphyric biosynthesis pathway is indicated: delta-ALA, delta-aminolaevulinic acid; PBG, porphobilinogen; ser, serine; gly, glycine, FH_4, tetrahydrofolate; CH_2=FH_4, N^5, N^{10}-methylene FH_4; CH_3-HF_4, N^5-methyl FH_4; homocys, homocysteine; S-AD-, S-Adenosyl-.

$R_1H \longrightarrow R_1CH_3$ indicates normal methylation (e.g., in choline and creatine formation).

$R_2H \longrightarrow R_2CH_3$ indicates abnormal methylation (e.g., of monoamines).

Summary

Four patients with an intermittent psychosis closely resembling hallucinogenic drug-induced states were suspected of having a porphyric disease and were investigated for a possible relation between the metabolic dysfunctions of porphyria and the psychotic syndrome. Theoretically the link could be in a disturbance of serine and glycine metabolism. This theory was supported by disturbances in serine and glycine excretion found in all patients during psychotic episodes. In addition, loading with one low oral dose of serine produced psychotic symptoms 5 h later which lasted 3-6 h. One patient reacted to glycine in the same way. These findings suggest that disturbed serine-glycine metabolism may have a key role in certain schizophreniform psychotic syndromes.

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CHAPTER III.

A PROPOSAL FOR A NEW CLASSIFICATION OF THE UNCLASSIFIED PSYCHOTIC DISORDERS. A RETROSPECTIVE STUDY *

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Introduction

Recently we postulated that an endogenous synthesis of hallucinogenic substances was likely to occur in some patients whose acute psychotic episodes clearly resemble a 'model psychosis' as known to occur after the intake of LSD, mescaline or psylocibine (1). In these patients a disturbance in the serine-glycine metabolism, the ultimate source of one-carbon moieties in the human body, is probably the cause for the generation of the psychotic symptoms (1) (2). An increased conversion of serine into glycine will result in an excessive formation of one-carbon moieties, which may result in an abnormal methylation or cyclization of mono-amines, of which several are potent psychotogenic substances (3).

Such an increased conversion of serine into glycine is thought to be the result of an increased pyrrol synthesis, which also occurs in porphyric diseases. So far porphyria could be demonstrated in only 20% of the patients studied (2).

When - after complete recovery - these patients, with or without porphyria, were orally 'loaded' with a single dose of serine, the characteristic symptoms, especially the sensory perceptual distortions, were evoked about 3-5 hours after ingestion. A few patients reacted to glycine in the same way. However, other patients who had also suffered from acute psychotic episodes, not accompanied by disturbances of sensory perceptions, did not react (2). This suggests that we are dealing with a separate entity of psychotic illness.

During our further search for similar patients, we realized that we could find

* Submitted for publication

them in the broad and ill-defined group of acute psychoses with an overwhelming variety of psychotic symptoms, mostly followed by a complete remission.
The DSM-III classifies these psychoses as schizophreniform, brief reactive, schizo-affective and atypical disorder, negatively delineated as 'Psychotic Disorders Not Elsewhere Classified' (4).
The occurrence of the special phenomena of a distorted sensory perception in some of these psychoses makes it possible to put forward a new and rather simple nosological approach for the unclassifiable psychotic disorders.
For the present paper we studied retrospectively the incidence of the anomalies of sensory perception and the psychotic states associated with it, in all case histories of unclassified psychoses available to us.

Material and methods

For the present study we collected and studied case histories of patients admitted to the psychiatric ward of the University Hospital during the years 1969-1979 who met the following criteria:

1. Detailed medical and psychiatric history, including clinical psychological reports, available;
2. Hospital diagnosis in concordance with one of the groups of the Unclassifiable Psychotic Disorders (the various diagnoses that are used for this type of psychoses in our hospital imply that the criteria for an affective or schizophrenic illness or paranoid psychosis were not fulfilled at the moment of discharge from the hospital);

To limit inclusion errors, special attention was paid to the following:

3. Good premorbid functioning;
4. Acute or subacute onset of psychotic symptoms;
5. Complete improvement, without signs of deterioration such as affective blunting, inertia, etc.;
6. Re-adjustment to the level of premorbid functioning without neuroleptic medication (lithium therapy allowed);
7. No mental retardation;
8. No organic factor(s) involved; cases with a deeply disturbed consciousness were excluded, perplexity was allowed;
9. No hard or soft drug use or alcohol abuse. No use of medication that could have contributed to the psychotic syndrome.

In the few cases when patient care and follow-up after discharge had not been carried out by our out-patient department, the necessary information to ascer-

tain diagnosis and/or complete recovery was obtained from attending physicians or from the 'Social-Psychiatric Service of Rotterdam'.
All doubtful case histories were omitted.

Evaluation and counting of symptoms

When a patient had been admitted more than once the best reported psychotic episode was chosen for analysis. Only unequivocal statements of the patients or described symptoms were taken into consideration.
In studying the case histories special attention was paid to the following aspects:

1. Statements of the patients concerning changes of sensory perception of surroundings (shapes, depth), light, colours, noises, smell and taste. These phenomena can cover a whole range from simple intensification of light and noises to gross distortion of the surroundings and synesthesias.
2. Perceptual changes of the stream of time. The subjective experiences included the simple acceleration of time passing as well as complex experiences as the running back of time and being frozen in time.
3. Strange bodily experiences. These cover minor changes of proprioception such as numbness, stiff muscles etc. to severe distortion of the body image, such as enlargement or shrinking of the head, being completely flat, having no legs, being transparent.
4. Depersonalization phenomena. To this category belongs autopsychic depersonalization (feeling empty, strange, etc.), derealization (the feeling as if surroundings or people have changed, are at a distance etc.), and somato-psychic depersonalization (my head feels empty, my legs feel as if they are of lead etc.).

   Although depersonalization phenomena frequently have a strong 'as if' character, the somato-psychic depersonalization made careful analysis sometimes necessary to decide to which category (3 or 4) strange bodily experiences belonged.

   To avoid wishful interpretation by the authors only direct statements were rated as true. Certain delusions and ideas uttered by the patient can point to a disturbed sensory perception but may have another basis as well. For instance 'Flowers and colours are so wonderful and have a special meaning' may indicate perceptual changes, but the statement can also result from the elevated state of mood of a manic patient without any sensory perceptual anomaly. The same holds for many hypochondriacal delusions.
5. Hallucinations (visual, auditory, olfactory, or tactile). Simple and unformed visual and auditory hallucinations were not rated when they were of short

duration (e.g. short flashes of light, sudden sounds only occurring once).

6. State of mood (anxious, depressed, elated, ecstatic). Only prevailing state(s) of mood lasting at least a day were rated. A sudden crying-fit in an elated patient was not considered to be a sign of depression.
7. Psychomotor disturbances (slowed down-hypokinetic; agitated-hyperkinetic; catatonic).
8. Bizarre delusions - the delusion of being controlled, or thoughts being known or read or eventually broadcasted, inserted or withdrawn - were also rated when present.

   The many other possible delusions or delusional ideas as delusion of reference, thought reading, being a powerful person, religious, paranoid and hypochondriacal delusions were so rapidly changing and abundantly present that counting proved rather superfluous and of little value. So only the 'suspect' delusions for a schizophrenic psychosis were taken into account.
9. Formal thought disorders as incoherence, concretism, and neologism.

A symptom was only counted once, even if it occurred at different intervals during the same psychotic period.
Special interest was also devoted to those cases showing a 'march of symptoms', which means a gradual development of psychopathological symptoms, especially the appearance and disappearance of certain symptoms during the development of the psychosis.
Attention was also paid to the precipitating factors. Although we tried to extract information on family psychopathology from the case histories, this proved to be impossible since exact information was often unavailable.

Statistics

Fisher's exact test and the Chi-square test were used to test differences between groups.

Results

To give an impression of the frequency of the psychotic disorders, the numbers of admission to our clinic from 1969 till 1979 were:

organic mental disorders	:	608
paranoid disorders	:	128
schizophrenic disorders	:	467
affective disorders	:	560
atypical/unclassifiable psychoses	:	340

It should be noted that these numbers are cumulative, repeat admissions being counted. From the 340 admissions of the last category, 133 patients were selected according to the criteria described in Methods.

Of these 133 cases, a total number of 62 patients were excluded: 11 were deemed to have schizophrenia; 10 ran a chronic course and needed prolonged (longer than 6 months) antipsychotic medication after discharge; 5 suffered from affective disorders with congruent psychotic features; 14 were judged to suffer from other psychoses, mainly paranoid and hysterical psychoses. In 14 patients organic factors, ranging from organic cerebral dysfunction such as epilepsy to general organic or hormonal diseases were involved. Eight patients were excluded because of language problems and lack of information.

On basis of symptomatology it was possible in the remaining 71 patients to discern two major psychotic entities and one minor one.

Twenty-seven patients showed a characteristic sensory perceptual distortion of light, colours, sounds, and surrounding spatial world (designated as group 1). One patient of this group was reported to have only suffered from perceptual distortions of shapes, while a second patient only suffered from a disturbed perception of light and colours. All other patients were reported to suffer from a variety of dysperceptions.

In 44 patients these symptoms were lacking, but in 35 patients (designated as group B) distinct depersonalization phenomena were present, which were severe in 24 patients.

Although depersonalization was also present in 11 patients of group A, it never dominated the clinical picture as was the case in most patients of group B.

Finally, a group of 9 patients remained, not showing dysperceptions nor depersonalization (designated as group C).

Age, sex, and admission

No differences were found with regard to sex within or between the three groups (an equal sex-distribution for all three groups: group A 13 male and 14 female; group B 18 and 17, and group C 4 and 5 respectively).

The age at the first psychotic episode varied widely in all groups, although the mean age for each group did not differ (see Table IA). The risk of a first psychotic outbreak seems relatively high in the second and third decade of life for group A and B (see Table IB). In addition, no differences were found for the mean duration of the index admission between the three groups (see Table IA).

The mean number of psychotic episodes occurring during the 10 years of the study is for group A 2.3; group B 1.8, and group C 1.4).

TABLE IA

AGE OF FIRST PSYCHOSIS AND LENGTH OF THE INDEX ADMISSION

	mean age of first psychosis	mean duration of admission in months
Group A (N=27)	28.4 (11-45)*	3.3 (1-7)*
Group B (N=35)	27.4 (15-40)	2.8 (1-7)
Group C (N=9)	31.4 (17-52)	2.3 (1-4)

* In brackets the range.

TABLE IB

AGE DISTRIBUTION OF THE FIRST PSYCHOSIS

Years	Group A	Group B
10-19	4	9
20-29	11	13
30-39	7	10
40>	5	3

Precipitating factors

In group A, sleep deprivation was considered to be a precipitating moment in 7 cases, menstruation in 2 cases, and other somatic factors (as operation, and somatic illness) in 3 cases.

For group B the numbers are respectively 4, 0, and 7.

For the remaining 15 patients of group A and the 24 patients of group B stressfull reactive and/or psychogenic moments were considered to be related to the outbreak of the psychosis.

The absence of any exogenous precipitating factor was clearly noted in one patient of group A, who had been admitted eleven times.

Hospital diagnosis

From Table II it is clear that the favourite hospital diagnosis for group A is degeneration psychosis and for group B psychogenic psychosis.

These are diagnostic concepts based on a typological approximation of form and content of the psychoses as observed during admission. They give a good impression of subtle differences and distinctions clinicians can make for diagnostic purposes, which are difficult to render by other means.

The differences of these diagnostic concepts are given in relation to the discussion of the new nosological classification proposed here.

TABLE II

HOSPITAL DIAGNOSES

	psychogenic psychosis	degeneration psychosis	atypical mania	schizo-phreniform psychosis	other
Group A	6*	10**	5	3	3
Group B	23*	4**	2	4	2
Group C	6	1	2	-	-

* chi-square 11.58, $p < 0.001$

** chi-square 5.72, $p < 0.02$

Symptomatology

Table III compiles the frequency of the symptoms for the three groups.

The similarities and differences between the two larger groups A and B are of special interest as the number of patients in group C is too small to allow a fruitful comparison and discussion.

No significant differences were found for distortions of body image or for an anomalous perception of the flow of time. However, from our study of the case histories we got the impression that the latter symptom had been often neglected during the psychiatric examination due to unfamiliarity with this type of symptom.

As far as hallucinatory experiences are concerned there is a significant preponderance of visual hallucinations in group A compared to group B ($p<0.001$).

In group B a negative mood (depression) obviously prevailed ($p<0.05$). Major mood swings (from depressed/anxious to elated/ecstatic or vice versa) were noted in all groups.

Most patients were considered to have shown a hyperactive motor behaviour. In addition, it is noteworthy that catatonic features in group A (7 out or 27 patients) were noted twice in a hyperkinetic patient and once in an akinetic patient. The same relationship was found in group B in which catatonia was present in 5 patients out of 35.

So-called suspect symptomatology for a schizophrenic process (formal thought disorders and bizarre delusions) was found in all groups. The main groups did not differ significantly in these aspects.

However, in group A this severe psychotic symptomatology was found to be present significantly more often in patients also sufferring from a distorted body image and/or catatonic symptoms (Table IV). Such a relationship could not be substantiated for group B.

In both groups perplexity does not seem to be related to the severe psychotic symptoms.

March of symptoms

A march of symptoms could be studied in 8 cases of group A. In these cases the development of symptomatology was more gradual instead of fullblown from the beginning.

For four patients a graphic representation illustrates this development of the changes in mood and motor behaviour, dysperceptions, distortions in body image, bizarre delusions and formal thinking disorders till the first signs of improvement (see fig. 1).

TABLE III

MAIN CHARACTERISTICS AFTER CLASSIFICATION INTO THREE GROUPS

	Group A (n = 27)	Group B (n = 35)	Group C (n = 9)
Distorted body image	13	14	3
Disturbances of time perception	12	7	-
Visual) hallu-	26*	19*	8
Acoustic) cina-	15	21	7
Olfactory + taste) tions	3	-	2
Depressed) m	6**	18**	4
Anxious) o	9	16	7
Elated) o	18	15	4
Ecstatic) d	9	5	2
Mood swings	7	9	4
Bizarre delusions thought disturbances	11	13	3
Perplexity	6	13	2
Hyperkinesia	9	13	7
Akinesia	3	4	0
Catatonic symptoms	7	5	3

* $Chi^{square} = 11.49$ $p < 0.001$

** $Chi^{square} = 4.32$ $p < 0.05$

Statistical evaluation of the other symptoms did not show any significant difference between group A and B.

TABLE IV

RELATIONSHIP OF SCHIZOPHRENIC SYMPTOMS AND DISTURBANCES IN BODY IMAGE, CATATONIC SYMPTOMS, AND PERPLEXITY

Group A		Body Image Disturbances		Catatonic Symptoms		Perplexity	
		absent	present	absent	present	absent	present
Schizophrenic Symptoms	present	2	9	5	6	10	1
	absent	12	4	15	1	11	5
		$Chi^2 = 6.31$		Fisher test		Fisher test	
		$p < 0.02$		$p < 0.01$		n.s.	

Group B		Body Image Disturbances		Catatonic Symptoms		Perplexity	
		absent	present	absent	present	absent	present
Schizophrenic Symptoms	present	8	5	11	2	10	3
	absent	13	9	19	3	12	10
		$Chi^2 = 0.046$		Fisher test		Fisher test	
		n.s.		n.s.		n.s.	

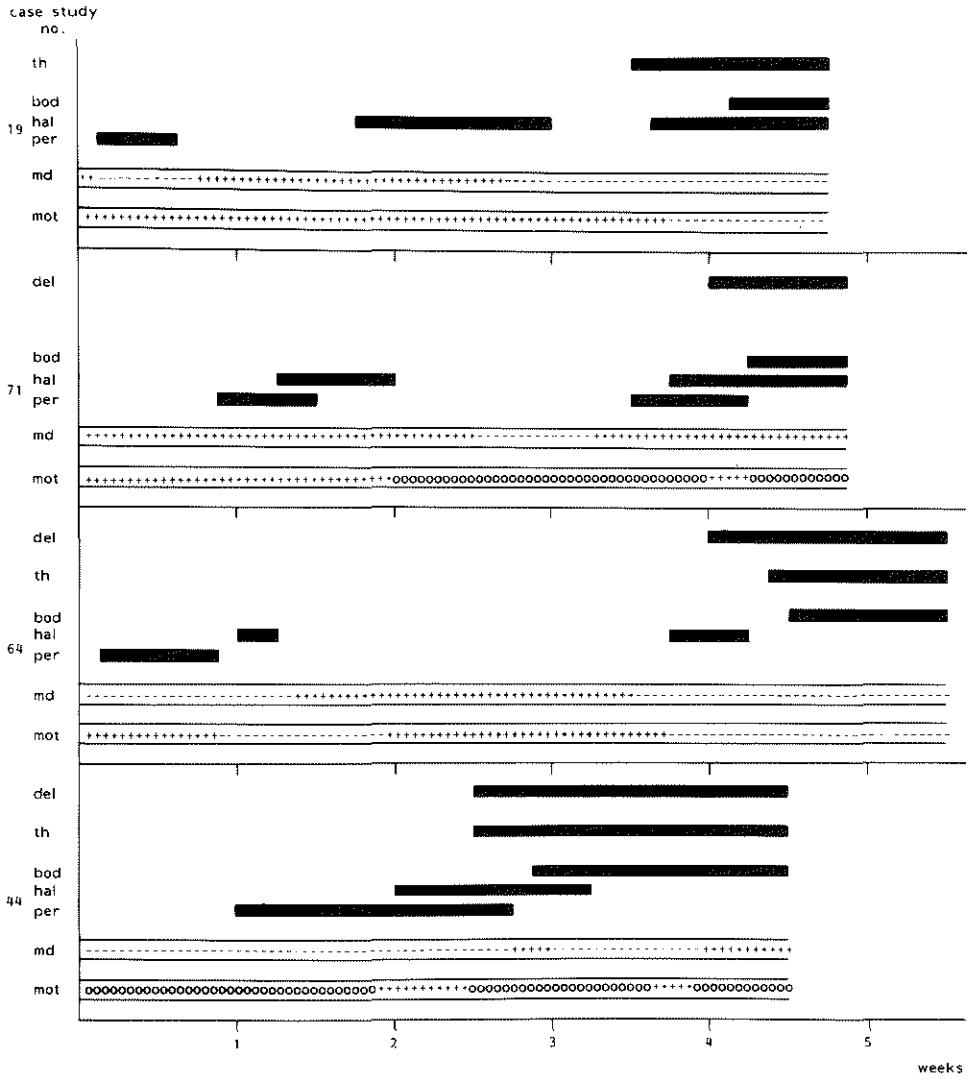
From these 8 cases it can be concluded that the sensory perceptual disturbances constitute early symptoms, although they can be preceded by disturbances in mood and motor behaviour. Hallucinations have been noted at a later stage and could be present throughout the further psychotic episode. In 5 cases visual hallucinatory experiences preceded the acoustic hallucinations. A distorted body image concomitant with bizarre delusions and/or thought disturbances, occurred later on. The finding that in this small number of patients 'suspect' symptoms were linked to a distorted body image is in agreement with the general conclusion that in patients of group A the severe psychotic symptoms are found to go with a distorted body image in one and the same patient.

Such a relation between mood and motor behaviour cannot be demonstrated in these eight patients.

A further analysis of the vicissitudes of the perceptual changes is given in Discussion.

A distinct march of symptoms could not be discovered in the patients of group B.

GRAPHIC REPRESENTATION OF THE MARCH OF SYMPTOMS OF 4 PATIENTS



del = bizarre delusions, th = formal thought disorder, bod = distorted body image, hal = hallucinations, per = distorted sensory perception.
md = mood; + indicates a positive, - indicates a negative state of mood.
mot = motor behaviour; 0 indicates a normal, + a hyperkinetic / desinhibited and - a hypokinetic / inhibited motor behaviour.

Dissipation of dysperceptions

The early presence of dysperceptions during a psychotic episode in patients showing a march of symptoms is in agreement with the presence of these symptoms during the first two weeks of the psychosis in other patients belonging to group A.

It should be noted that almost all patients had been treated with neuroleptics which also may suppress the dysperceptions.

However, in two patients (nr. 64 and 71) with a march of symptoms who did not receive neuroleptics, the dysperceptions disappeared spontaneously.

In contrast, sensory perceptual distortions were clearly present throughout the whole psychotic episode in two patients despite neuroleptic treatment.

DISCUSSION

Much attention has been paid to the acute and difficult to classify psychotic disorders, since Kasanin's publication in 1933 of what he called the schizo-affective psychoses (5), although such a group of psychoses had been described long before Kasanin (6).

There is serious doubt whether these so-called schizo-affective psychoses form a group of separate psychotic illnesses not related to the two functional psychoses (7).

The numerous studies on this problem of the 'third functional psychosis', start from a symptomatological approach, namely a temporary mixture of 'schizophrenic' and 'affective' symptoms, which is regarded as sufficient to classify this complex as a psychotic entity (7).

Genetic, (8-10), family (9-13), and follow-up studies (14-17) subsequently suggested that the group of schizo-affective psychoses is a heterogenous one related to the Manic-Depressive or Schizophrenic Disorders or to both in varying degrees. Several authors point out that most of the so-called schizophrenic symptoms, when observed together with affective, especially manic, symptoms have little value in predicting a chronic deteriorating course, and conclude that the patients actually suffer from a manic-depressive illness (18-27).

In a thorough overview and reassessment of the literature on the specificity of 'schizophrenic' symptoms, Pope and Lipowski (28) also suggest that the major part of the schizo-affective disorders are to be considered as a variant of Manic-Depressive Illness.

Few arguments are apparently left to establish the schizo-affective and related disorders as the third functional psychosis.

Consequently, as most authors regard degeneration (29-31), atypical (32), cycloid (33, 34), psychogenic/reactive (35), schizophreniform (36), or schizophrenia-like emotional psychoses (37) etc. as simple eponyms of schizo-affective psychoses, these diagnostic labels are only of descriptive and limited value. The lack of homotypical morbidity among family members (9, 13) and the metamorphosis of successive psychotic episodes in individual patients from 'schizophrenic' to 'manic' (23, 26), are in support of such a point of view.

It is doubtful whether such a far-reaching conclusion is justified.
Firstly, in the studies (8-17) of syndromes of schizo-affective psychoses, too little attention has been paid to the benign course of the disease, namely the complete recovery from a psychotic episode, which is a fundamental characteristic of this type of psychoses. Secondly, specific descriptive-diagnostic concepts of these psychoses, as described below, are neglected.
In the reactive/psychogenic psychoses of McCabe (35) the onset is acute and associated with an adequate trauma or emotional conflict that is reflected in selfdepreciation, referential ideas and persecutory delusions. The patient is depressed, anxious and irritable. Motor activity is generally normal. Auditive hallucinations and first-rank symptoms of schizophrenia occur in a state of clear consciousness. More florid symptomatorogy is associated with a perplexed or confusional state.
In the cycloid psychoses of Leonhard (33) and Perris (34) a greater variety is found: the syndrome is characterized by mood swings and various degrees of confusion, paranoia-like symptoms and/or hallucinations not syntonic with the level of mood, motility disturbances, episodes of ecstasy and pananxiety.
Taking the clinical description into account, the cycloid psychoses are possibly the same as the atypical psychoses described by Mitsuda (32) who stresses the rapid fluctuations and kaleidoscopic pictures. Delusions and paranoid-hallucinatory experiences are found together with confusional or oneiroid states.
Although McCabe reported that some of his patients had relatives with affective psychoses (35, 38), all authors find that the genetic part of their studies supported the notion that these groups of psychoses form an independent entity.

With the above mentioned, more narrow definition of reactive, cycloid and atypical psychoses in mind, it is possible to distinguish many of the acute psychoses with a favourable outcome from the unclassifiable psychoses.
However, these diagnostic concepts are still based on a typological approach and pathognomonic symptoms supporting a straight classification are not found (39).

The present study shows that difficult typological characterization is not necessary and that the group of unclassifiable psychoses can be differentiated by using simple criteria, into at least two separate groups of psychotic disorders: a psychosis characterized by a temporary, distorted sensory perception (group A), and a psychosis characterized by distinct depersonalization phenomena without these distortions (group B).

Group A: Psychoses accompanied by distorted sensory perception

Due to the extensive case notes and the interest of our clinic in depersonalization and related phenomena (40, 41) it was possible to identify such a sub-group without great difficulties.

In all patients perceptual anomalies were observed at the start of the psychotic period (first and second week), except for two patients who kept complaining about distorted perception during the total length of their psychosis.

If the dysperceptions are indeed caused by an endogenous synthesis of hallucinogenic substances the question arises why these disturbances disappear after a few weeks. The only model psychosis comparable to a naturally occurring psychotic state is that induced by hallucinogens administered continuously for weeks or months (42). From animal studies evidence has been presented for the rapid development of tolerance to the inhibitory but not to the excitatory effects of LSD and mescaline (43, 44). It has been suggested that this inhibitory effect is comparable to the rapid development of tolerance to psychedelic effects of drugs in man (42, 43, 44).

Tucker et al. (45) presented some evidence for an increase in pathological disturbances of thinking in non-schizophrenic subjects after prolonged use of hallucinogenic drugs. This suggests that at least in some individuals, adaptation to psychotomimetic effects is lacking.

Besides the development of tolerance to hallucinogenic substances as a possible cause for the disappearance of these early symptoms, the capacity of the CNS to adapt to an altered sensory input, has to be taken into account (42). The latter can be illustrated by experiments with human subjects making use of prismatic or coloured lenses (46). The effect of neuroleptics on these disturbances is obscure.

The altered sensory perception also forms a basis for a highly personal, but psychotic interpretation, in which the changes as experienced by the patient will be concealed. Thus, one patient stated that she was going to be raped by an ape, while it became clear afterwards that she experienced the persons around her as dark hairy-like individuals resembling apes. The statement of another patient 'I

am in paradise' was based on the perception of magnificent intensified colours, as told by this patient afterwards.
Besides, in this totally altered mental state otherwise repressed intrapersonal conflictuous and primitive drive material is released (47) and can be so overwhelming for the patient that other experiences are suppressed.
It is conceivable that the experienced perceptual changes are less and less directly mentioned by a patient after continuation or worsening of the psychosis. It is likely that these perceptual changes may become interwoven with, and partly constitute, the actual content of the psychosis.
In order to identify this type of psychosis, it is therefore of paramount importance that patients be questioned about sensory perceptual disturbances.

The march of symptoms

Some of the psychoses from group A (8 out of 27) were found to have a gradual development of symptomatology. The recognition of such a march of succeeding stages, each with its characteristic symptoms, may have several advantages.
Previously (1, 2) we used a scheme adapted from Fisher (48) which encompassed a gradually developing symptomatology with the sequence of anxiety, dysphoria/euphoria, depersonalization, dysperceptions, hallucinations and catatonia, while delusions, negativistic behaviour etc. were considered as secondary phenomena which had no direct impact on assessing the severity of the psychotic illness.
Further studies have made it clear, however, that this scheme is rather oversimplified and is often not applicable. From a phenomenological point of view, disturbances of mood are not of the same order as disturbances in perception or motor behaviour, although they may be closely related. Bizarre posturing may be the consequence of the perception of severely distorted surroundings as a lack of vision of depth, but such a distorted perception may occur without bizarre posturing in other patients. Positive changes in mood may be associated with hyperactive motor behaviour, as for instance in a manic syndrome, but the opposite can also be demonstrated. The experience of speeding up of the stream of time is mostly accompanied by a cheerful, elated mood and hyperkinetic behaviour, but some patients may be completely akinetic and apprehensive although they experience the same acceleration of the passage of time. As has been observed for personality factors involved in LSD-induced states (49), cognitive and biological factors may also influence and shape such a temporary combination of symptoms.

Therefore, we have looked more carefully into the categories of psychopathologic changes which we thought to be of fundamental interest to understand the diversity of the clinical pictures observed.
We did so for the basic disturbances in a) sensory perception, b) time perception, c) mood and d) motor behaviour.

a) Sensory perception.

From the detailed clinical descriptions of the patients with a march of symptoms, we can compose within the category of sensory perceptual disturbances, the following sequence of psychopathological phenomena as they emerged during the progression of the psychosis:

1. Perceptual changes of light, colours, sounds, taste, proprioception.
2. Perceptual changes of the surrounding spatial world.
3. Visual hallucinations.
4. Auditory hallucinations.
5. Gross disturbances of the body image, that result from extreme disturbances of proprioception.

Of this sequence, the symptoms mentioned under 1. and 2. tended to disappear while the remaining symptoms could be observed during the whole psychotic episode.

From the material studied we tentatively conclude that an increasing visualization, such as closed eye imagery, more vidid and colourful dreaming, eidetic memory and finally visual hallucinatory experiences, occured at the cost of conceptual thinking. Conceptual thought can be completely perceptualized with the impossibility to understand and to give logical information. Logic thinking is blocked, concepts become percepts.

One example may suffice: A patient was asked from what angle he looked at his problem. It turned out to be impossible for him to understand the figurative meaning of this phrase, because he saw images in which he was fishing ('angling') and he gave some seemingly non-sensical answers. Although such a relationship is not always so clearly understandable, the results show that a distorted body image can be associated with formal thought disorder and/or bizarre delusions.

The impairment of the conceptual world at the cost of perceptualization makes it tempting to speculate that an increasing activation of the non-dominant cerebral hemisphere is responsible. Such a mechanism has been suggested to explain the symptomatology of hallucinogenic drug-induced

states (42).

The high incidence of auditory hallucinations in group A may contradict the hypothesis that the endogenous synthesis of hallucinogenic compounds is responsible for this type of psychosis, since the use of a hallucinogenic drug is mostly associated with visual perceptual phenomena. However, Young (50) reported a high incidence (30%) of auditory hallucinations in LSD-induced states.

b) In the same manner we studied the experiences of the passage of time.
A distinct sequence of abnormal perceptions of time was not observed in our material. Nor was it evident that the more bizarre disturbances of time perceptions were related to the more severe disturbances in sensory perception. As mentioned under Results, the data of these disturbances are insufficient to draw conclusions.

c) A gradual development of mood disturbances from depression, anxiety to euphoria, elation and finally ecstasy, has not been noted. The changes in the state of mood seemed to occur abruptly (mood swings).

d) The same applies to motor behaviour. Hyperkinetic and catatonic features dominated the clinical picture in the individual patient. Extreme hypokinesia (akinesia) was seldom noted.
When catatonia was present it was noted to occur in the more severely psychotic patients belonging to group A, while this correlation was lacking in patients of group B. No other clearcut relationships with sensory perception or mood could be found.

Although it was not possible to demonstrate either a relationship between mood disturbances and motor behaviour, and the sequence of sensory perceptual distortions or a predictable development of symptomatology within these categories, the presence of these disturbances is very relevant to the often confusing diagnostic excercises in the group of unclassified psychoses.

Cognitive changes

The effects of these changes are far-reaching. A new cognitive restructuring and re-appraisal of the changed inner and outer world has to take place. Many patients, mainly those characterized by the diagnosis 'degeneration psychosis', may experience objects and happenings as having new and special meaning, they have become symbolic or allegoric, refering to a divine cause which only the patient is able to grasp. Past and future can merge into an all encompassing

experience of one-ness. It is a rich, mythical experience, comparable to that induced by hallucinogenic drugs.
During progression of the psychosis many, mostly perfunctory, bizarre ideas and delusions arise.
In order to adapt to and comprehend the dramatically changed stream of information from the outer, but also from the inner world, ideas and delusions of reference, grandiosity, hypochondria etc. may develop. Consequently, delusions will not be of primary but most probably of secondary derived nature.
One of the patients experienced that suddenly time came to a standstill and started to run back. Thus this patient developed the delusion that he was immortal and would go back in time untill the birth of the universe and then would live with God. In order to stop this process in a very concrete manner he annihilated Time by destroying the ward clock.
However, when the fundamental changes are very severe and/or the cognitive abilities of the patient are poor, such an adaptation is likely to fail, leaving the patient perplexed.
In relation to the march of symptoms it is interesting to note that bizarre delusions such as being able to read thoughts or having one's thoughts read and sometimes thought sharing and broadcasting were also observed when the final stages of the perceptual scheme (4. and 5.) were present. Body and ego bounderies are broken down simultaneously.
In general it can be stated that a more florid and even suspect schizophrenic symptomatology belongs to the final stages.

The composition of different psychotic states

Based upon the basic psychopathological changes (perception, time, motor behaviour, mood) it is possible to reduce apparently different psychotic states to the same denominator. Different psychotic states appear as a resultant of changes in the composition of the basic psychopathology.
This can be illustrated by the following examples:
During her first admission a patient showed an (atypical) manic syndrome. She had delusions of grandeur with rapid speech characterized by loose associations. According to her, everything went very fast due to an acceleration of time. Everything around her appeared happy and gay, light and colours seemed very bright and objects showed beautiful, coloured outlines. During her second admission she was very anxious, complained of strange bodily experiences and suffered from hypochondric fears. She felt that everybody knew exactly what she

was thinking. Time had slowed down, but in contrast everything outside her was moving very fast. In addition, bizarre motor behaviour was observed as well as concretistic statements. A schizophreniform psychosis was diagnosed. Although there was no remark suggesting a distorted perception of colours, sounds, and surroundings, she mentioned afterwards that before her admission everything had been enveloped in a red fog.

A patient became perplexed when a mixture of rich hallucinatory experiences together with akinesis and a very rapid passage of time was present. This clinical picture favoured the diagnosis of an oneiroid state. However, a later psychotic episode of the same patient had been labeled as atypical mania.

In another patient anxiety, dysperceptions, depression, and hypochondric fears emerged after the death of a beloved person, due to cancer. The diagnosis of psychogenic psychosis was therefore made.

In conclusion, a 'classic' diagnostic label does not guarantee that the psychosis of the patient is neither variable nor reproducible. It follows that the diagnosis of acute psychoses according to current criteria will not result in a homogenous group of patients.

The most frequently used diagnosis in this cross-sectional study was degeneration psychosis. In our clinic this type of psychosis is characterized by mythical experiences, ecstatic feelings, often with sudden changes of mood. Multiple perfunctory delusions and hallucinatory experiences are present. The contents of the psychosis are often not related in a clearly 'understandable' way to preceding conflicts, psychotraumas etc.

The clinical picture as a whole can be described as kaleidoscopic and polymorphic and is in our opinion identical to Mitsuda's atypical psychosis or Leonhard's cycloid psychosis, especially the anxiety-happiness psychosis (33) and the ancient 'bouffée délirante' (51).

Group B: Psychoses without a distorted sensory perception

As a result of the creation of group A a second group, group B, emerged. In these patients a distinct and often severe depersonalization was found to be a striking feature. It is not inconceivable that this group also constitutes a homogenous entity. The most common diagnostic label in this group of patients was psychogenic psychosis, which may be indicative of a homogenous entity. Although in group A depersonalization was also noted, it was not found to be such an all pervading state as in group B.

The clinical picture of group B, especially the delusional contents, is more

stable. The terms unpredictable, polymorphic and kaleidoscopic do not apply to this type of psychosis, hence the diagnosis degeneration psychosis is seldom found in this group.

In accordance with the definition of a reactive psychosis by McCabe (35) the contents of these psychoses were clearly related in a more understandable way to preceding emotional turmoil.

Significantly less visual hallucinatory activity was found, whereas disturbances in time perception and especially changes in body image were not significantly different from those found in group A.

These findings are in agreement with those by Freeman and Melges (52), who showed that in acute psychoses self-estrangement (comparable with our auto-psychic depersonalization), and disturbed time sense are mutually dependent phenomena.

The disturbances in body image of this group can not be understood as based on disturbances in proprioception. In a state of depersonalization, perception itself is intact, but the incoming information is detached, dissociated from the normally attendant feelings, memories, body scheme etc. It is the apperception that is failing. But this will finally result in an identical symptomatology as encountered in group A. Not only the own body will appear to be changed, but also in this group all incoming information can become so uncommon and strange, that it will result in a complete state of perplexity which, as we noted, is mostly accompanied by a misrecognition of individuals. Perhaps other clinicians will diagnose a state of confusion, but we agree with Cutting et al. (53) who separate these superficially identical states, because of the connotations of the term confusion with the organic brain syndromes.

In contrast to group A there are no indications that the more severe psychotic symptomatology (disturbances in body image, 'schizophrenic' and catatonic symptoms) are concentrated in individual patients.

Although positive mood states are also present in group B, feelings of depression significantly dominate the clinical picture. Mood swings are also found in this group. According to the case notes, the diagnosis of an atypical form of (manic-)depressive psychosis has been often considered.

We have no certainty that this can be ruled out. It is possible that this group is genetically related to the bipolar affective disorders. The available data on familiar diseases are too weak to confirm or to refute this possibility. However, the non-congruency of typical delusions and hallucinations with the state of mood, as occurs in psychotic depressions (melancholia), apparently favoured the final diagnosis of psychogenic psychosis.

CONCLUDING REMARKS

Anomalous sensory perception and psychedelic experiences have attracted much attention in relation to the psychopathology of schizophrenia (54-57), undefined acute psychotic states (58), and hysterical psychoses (59). This resemblance is partly responsible for the idea that a hallucinogenic drug-induced psychosis could be an appropriate model for schizophrenia. As postulated by Osmond and Smythies a metabolic fault, e.g. the dysmethylation of mono-amines, could be the cause of schizophrenia (60). Up till now no solid proof has been found for such a hypothesis.

The same idea has found too little consideration in the groups of episodic psychotic illnesses, which is undoubtedly the result of the fact that for a long time schizo-affective and related disorders were considered variants of schizophrenia, while nowadays they are considered variants of manic-depressive illness. The obvious heterogenity of this group of psychotic disorders seems in a large measure responsible for the confusion.

However, in our opinion at least one group of acute psychotic psychoses with complete recovery (group A) can be distinguished as a separate entity.

Group A is characterized by sensory perceptual distortions and shows in general a kaleidoscopic, polymorphic clinical picture.

A second group (B) lacks these features and is characterized by profound depersonalization, a more depressed mood and further a less wild, more monomorphic clinical picture.

Close to our devision in A and B, are the ideas of Roth (61) on schizo-affective psychoses. He also reported that two groups of schizo-affective psychoses can be distinguished. His first group is characterized by a short-lived schizophreniform illness. He relates these psychoses to the phobic-anxiety depersonalization syndrome which is known to occur as a reaction to calamitous, stressful events in anxious, oversensitive, selfconscious patients lacking in self esteem and suffering from varying degrees of phobias. Most of the patients of the phobic-anxiety depersonalization syndrome suffer from various degrees of depersonalization and 37% of 135 patients had 'temporal lobe features' (62), which include the sensory perceptual anomalies and time sense disturbances described for group A in the present paper. According to Roth the remaining group has much more in common with the bipolar affective disorders.

The current classifications of the psychoses with an acute onset and benign

course are based upon rather complex diagnostic concepts with all their disadvantages.

The classification presented here offers the possibility to disregard these difficult diagnostic concepts, which are often hard to replicate in practice. The 17 patients in group A with another label than degeneration psychosis would go unnoticed, a number far too large to be overlooked.

In conclusion, we can state, that the positive identification of one group of psychoses characterized by sensory perceptual distortions simplifies and improves the classification of the 'unclassifiable' psychotic disorders.

SUMMARY

We restudied the case histories of all patients admitted to the University Hospital Dijkzigt Rotterdam (1969-1979) and belonging to the group of 'unclassifiable psychoses' in an attempt to define a homogenous group of psychoses within this broad and poorly delineated category of disorders. Only those psychotic states were included, which exhibited distorted sensory perceptions resembling hallucinogenic drug-induced states, disregarding the current typological characterization of the clinical picture.

Twenty seven patients out of 71 presenting acute psychoses with complete recovery, were found to show clearly the desired characteristics. Insight in the composition of the diverse clinical pictures on a phenomenological basis has been obtained. Many psychotic states of this group showed a clinical picture that can be described as polymorphic and kaleidoscopic, previously reported in the literature as 'bouffée délirante' (51), atypical psychosis (32), and cycloid psychosis (33).

A second, slightly larger group emerged, characterized by profound depersonalization and further by a depressed mood and more stable clinical picture. This group may be related to the affective disorders, although for several reasons the label psychogenic/reactive psychosis seemed more appropriate.

This classification may prove to be useful in many fields of investigation but at present the main focus of the authors' studies is the endogenous formation of hallucinogenic substances by metabolic disorders in acute non-schizophrenic psychoses.

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CHAPTER IV.

INDUCTION OF PSYCHEDELIC AND PSYCHOTIC SYMPTOMS BY ORAL SERINE AND GLYCINE LOADING IN PATIENTS WITH EPISODIC PSYCHOSES. A DOUBLE BLIND STUDY *

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INTRODUCTION

Previously we described four patients suffering from an acute schizophreniform psychosis characterized by multiple sensory perceptual disturbances, who reacted with typical symptoms of distorted perception, depersonalization and changed state of mood after oral administration of a single dose of serine (2 mmol/kg body wt.). One patient also reacted to glycine (1).
We suggested that in these patients the psychosis was due to a disturbance of serine-glycine metabolism, yielding great quantities of one carbon moieties, which may react with monoamines to form hallucinogenic substances. Cyclization of monoamines producing beta-carbolines and isoquinolines, several of which have psychotogenic properties, is now thought to be more likely than faulty methylation (2, 3, 4). This cyclization of monoamines is thought to be the result of a non-enzymatic condensation of formaldehyde with monoamines.

Other patients were clinically recognized by the presence of the sensory perceptual anomalies (dysperceptions) which are identical with the distorted perceptions experienced during hallucinogenic drug-induced states.
The acute onset and the benign course of the psychoses, with complete recovery after each episode, are also distinctive of this group. In addition, many patients did not seem to respond favourably to neuroleptics but improved on a high carbohydrate, low protein and low fat diet (5).

* Submitted for publication

To demonstrate the assumed disturbance in serine-glycine metabolism it was predicted that such patients, after recovery from their psychosis, would react with hallucinogenic drug-like symptoms after administration of serine (2 mmol/kg body wt.).

In this report we present the clinical findings of serine, glycine and glucose loading tests performed in a double blind fashion in several categories of patients who had suffered from acute psychotic episode(s) with and without distortions of sensory perception.

MATERIAL AND METHODS

General design of the loading test

The loading tests were performed on the ward after complete remission of the psychosis had been established with the exception of group 2b, representing schizophrenic patients in the residual phase.

The patients had not taken psychotropic medication for at least two weeks, except that concomitant use of lithium was allowed in some.

For each patient three powders were prepared, one with serine, one with glycine, and one with glucose. In some patients glucose was replaced by L-methionine and/or L-alanine as indicated in Results. Doses were fixed at 2 mmol/kg body weight.

The powder was dissolved in yoghurt and given before breakfast. Patients lay on their right side for 30 minutes to increase gastric emptying and the rate of absorption.

The loading tests were performed double blind, patient, psychiatrists, and nursing staff, being unaware of the sequence of administration of the test substances.

Therefore the patient was observed during the whole day. After normal behaviour was established, after one or two days rest, another powder was administered.

In most patients the loading tests were performed while they were on a constant high carbohydrate, low fat, low protein, diet. The amounts of serine and glycine in this diet have been calculated (2,3 and 2 gram respectively), in order to study the serine-glycine conversion by means of hourly blood samplings. The results of these analyses will be published separately.

For a group of 21 patients (1a) the code of the sequence of administered powders was broken after all these patients had completed the trial. Otherwise the code was broken after each individual trial.

Selection of patients

Three main groups of patients have been distinguished:
Group 1a: 21 patients admitted and observed in our hospital for an acute psychosis who showed complete recovery. The diagnostic criteria for an affective, schizophrenic, or paranoid disorder were not fulfilled in these patients. According to DSM-III criteria most of them fit into one of the sub-categories of Psychotic Disorders Not Elsewhere Classified. In addition, these patients all suffered from sensory perceptual distortions such as of light, colours, sound(s), shapes, vision of depth, during or previous to the psychotic episode. These patients were predicted to react with characteristic psychopathological changes to a serine load, performed after complete recovery of their psychoses.
Patients with organic factors like porphyria which may be causally related to the psychosis, were not excluded from this trial, unless clouding of consciousness (e.g. delirious states) was a central feature.

Group 1b: the patients complied with the same diagnostic criteria as those mentioned under 1a, but were admitted after the first trial of 21 patients (1a) or had been admitted and observed elsewhere. In the latter case the perceptual anomalies were retrospectively assessed. These patients were also predicted to react to serine.

Group 2a: patients having suffered from acute psychoses with complete recovery, who had also shown sensory perceptual distortions. However, a pathogenesis other than a disturbed serine-glycine metabolism was held responsible for the psychoses. They were diagnosed as suffering from: minimal brain damage, tryptophan malabsorption, temporal lobe epilepsy, LSD-abuse, and borderline state. These patients were predicted not to react.

Group 2b: patients suffering from a residual (defective) schizophrenic state, but who during an acute episode ('Schub') had reportedly shown disturbances of sensory perception. They were also predicted not to react to serine.

Group 3: acute psychotic patients, who gained full recovery, but had not exhibited the perceptual changes. Organic psychoses were excluded. These patients were predicted not to respond to the serine load.

Group 4: 15 healthy persons (students and nurses) without a personal or a family

history of psychoses, were loaded.

All patients had had a routine laboratory investigation of hepatic and renal function, blood cell counts etc. Blood plasma levels of folic acid, vitamins B_1, B_6, B_{12} were determined to exclude deficiency. During the psychotic episode porphyrin and porphobilinogen excretion in urine was measured.
As soon as the clinical condition made it possible, electro-encephalography was performed.

Observation of patients during the loading tests

The Ethical Committee of the University Hospital Rotterdam 'Dijkzigt' agreed to the test as described above. Patients who consented to participate were informed in a general way, stating that a mental change might possibly occur without emphasizing any specific psychopathological symptomatology in order to prevent induction and unnecessary apprehension.
To prevent a laboratory-like observation method, which may considerably influence the outcome (6), the physicians and nurses tried to observe as inconspicuously as possible. The daily routine of the patients, like creative therapy, reading, short walks, etc. was interrupted as little as possible.
When any change was observed, the patient was encouraged to report it openly. When necessary the patient was reassured about the symptoms and their duration. Every reaction reported or observed was noted as well as the moment of the first symptoms and the lenght of the reaction.
In a semi-structured interview after each loading day, the changes were assessed and the patients completed the Experiential World Inventory of El Meligi and Osmond (7), which most of them found helpful to compile their experiences.
To comprehend the manifold results, a scheme slightly adapted from Snyder and Lamparella (8) has been used, covering all phenomena observed (see Table I).
Only those patients showing distinct psychopathological changes were considered positive (see Results).

RESULTS

The results of the positive reactions after serine or glycine loading are compiled in Table I. When different reactions were observed to both aminoacids of after a repeated loading test later on, the strongest is found in the table.
P 1-4 are the patients described previously (1).

P 5-16 are patients from group 1a, P 17-22 are from group 1b.
C_1 and C_2 are patients (from group 3) showing effects, but were not predicted to do so.

General characteristics of the patients showing psychopathological changes after serine/glycine loading.
The mean age of the first psychotic episode was 24 years, the range 15 to 47 years. The average duration of the index admission (=last admission before loading) was 3.1 months (range 1-12 months). The mean number of psychotic episodes of these patients was 2.9 (ranging from 1-10). The mean age at which the first loading took place was 27.6 years (range 18-48 years).
Fifteen out of 24 patients were women. Hospital diagnosis at discharge varied: degeneration psychosis was diagnosed in 10, schizo-affective and other psychotic states in 7, psychogenic psychosis in 4 and schizophreniform psychosis in 3 patients. These hospital diagnoses are discussed elsewhere (9) in relation to the problems of the Unclassifiable Psychotic Disorders (DSM-III).
The 'spontaneous' psychoses often followed an emotionally stressful period. It should be noted that during such periods lack of sleep and poor appetite are commonly reported. In addition, in 5 patients a period of voluntary starvation (slimming diets) preceded the outbreak of the psychosis (P 5, P 6, P 14, P 16 and P 17). In three women the psychosis started during the premenstrual period (P 3, P 22 and C 2).

Plasma vitamin levels and renal function were found to be within normal limits in all patients. An abnormal discharge pattern of temporal lobe origin was found to be present in patients P 8 and P 12.
The interference of organic factors in some patients (P 2, 4, 12 and 18) with their psychoses and loading tests will be discussed below. In all other patients normal liver function tests were found.

The serine and glycine-induced reactions

As can be seen from the table I the types of reaction differed widely among the patients. Different responses were observed in those patients who underwent the loading test procedure for a second time after another psychotic episode (P 4, P 6, P 12, P 16). Three patients (P 9, P 15, P 20) did not report changes in sensory perception. Six patients showed only psychopathological sequela after a glycine load (P 5, P 9, P 13, P 17, P 18, P 21). Three patients (P 1, C 1 and C 2)

TABLE I. SCHEMATIC REPRESENTATION OF PSYCHOPATHOLOGICAL CHANGES AFTER SERINE AND GLYCINE LOADINGS.

	reaction to			Sensory perceptual distortions							Mood		Motor behavior			Cognition			Ego Control		
Patient nr.	serine	glycine	somatic symptoms	light, colours, sounds	shapes, distances	enhanced imagery	hallucinations	proprioception	body image	time sense	positive	negative	hypomotility	hypermotility	catatonic features	new insights, paranoid ideas	frank delusions	loss of concentration	estrangement, depersonalization	feelings of desintegration, impuls dysregulation	REMARKS
P 1	+	+			+			+		+		+	++					+	++		
P 2	+		+	+	+		+				++			+					+		porphyria variegata
P 3	+			+	++		±				+	+		+		+				+	
P 4	+		+	+	+		+	+		+	+	+	+					+	+		porphyria cutanea tarda, loading test repeated, also Ala and Meth loaded
P 5		+	+	+	++	+				++	++			+		+					
P 6	+		+	+	+					+	+	+	+			+			+		loading test repeated, also Ala and Meth loaded
P 7	+		++	+								+		+	+		+		++	+	
P 8	+			+						+	++			+			+			+	
P 9		+	+					+		+		+	+			+		+	++	+	
P 10	+				+			+		+		+	+					+	+		
P 11	+		++	+	++			+	+	+	+		+			+				+	
P 12	+		+		+	++						+	+					+	++	+	liver disease, loading test repeated

	patient nr.	C 2	C 1	P22	P21	P20	P19	P18	P17	P16	P15	P14	P13
reaction to	serine	+	+	+		+	+			+	+	+	
	glycine	+	+		+			+	+				+
	somatic symptoms	+		+	+	+	+	++	++	+	++	+	
Sensory perceptual distortions	light, colours, sounds	+	+	+	+		+	+	+	+		+	+
	shapes, distances	+	+	+	+		+	+	+				+
	enhanced imagery				+				++				
	hallucinations												
	proprioception			+	+	+	+						
	body image												
	time sense	+		+			+		+	+		+	
Mood	positive		+				+			+	+		+
	negative	+		+		+		+	++			++	
Motor behavior	hypomotility			+		+				+			
	hypermotility	+	+								+		+
	catatonic features												
Cognition	new insights, paranoid ideas		+	+	+						+	+	+
	frank delusions	+											
	loss of concentration			+			+						
Ego Control	estrangement, depersonalization			+						+	+		+
	feelings of desintegration, impuls dysregulation	+		+				+	+			+	
REMARKS		patient was not predicted to react (see text)	patient was not predicted to react (see text)	lithium therapy, also Ala loaded		also Ala loaded		liver disease	lithium therapy	loading test repeated, also Ala loaded			lithium therapy

reacted to serine as well as to glycine.
As far as can be concluded from the present results, lithium administration in P 13, P 17 and P 22 and the diet in P 1-9 and P 12-17 (as mentioned under Material and Methods) did not impair or alter the evoked reaction pattern in comparison with the other positive loadings.

The first signs of the reaction were observed between 2 and 5 hours after administration of an aminoacid; the reaction itself lasted at least 3 hours, but always subsided the same day. In many patients the reaction developed along a clearly recognizable pattern: the patients first complained of warmth, dizziness, lightheadedness, or nausea. Wide pupils, reddened faces and sweating were seen.
This was followed by sensations of estrangement and depersonalization, being unstable, feeling heavy or light and the idea that time was speeding up or slowing down. After this, distinct disturbances in sensory awareness of light, colours and sounds emerged, and finally an anomalous perception of contours, shapes etc. and disturbances in proprioception. Mood had by then became elated or anxious/ depressed.
In a few patients enhanced imagery, like vivid closed eye imagery and hallucinatory experiences were observed at the height of their experience. Personality factors, anticipation, previous experiences gave form to the ultimate pattern (see Discussion).

Reactions to Glucose, Alanine and Methionine

One patient out of group 1a showed a distinct reaction pattern beginning three hours after administration of the powder and lasting for six hours. Strong motor inhibition, slurred speech, anxiety, paranoid ideas were observed next to subjective reports of a slowing down of the experience of the flow of time and extreme depersonalization.
Code breaking revealed that glucose had been given that day (blood analysis confirmed this), no reactions were noted to serine and glycine.

Almost 30 percent (10 out of 31) of the patients who were predicted to react, complained during (a) loading day(s) about feelings of apprehension and showed vegetative symptoms like perspiration and stomach ache on powders that otherwise did not evoke mental or perceptual changes, and therefore were not considered to be responders.

Five serine positive patients were subsequently loaded with L-alanine and two of them also with L-methionine. The glucose responsive patient also underwent both additional loadings.
No reaction was observed after loading with alanine, and, though no mental change was observed after methionine, the patients complained to a varying degree about feelings of sickness and warmth, were perspiring and some had an ill-looking, greyish complexion. Therefore we decided to stop further methionine-loading tests.

The loading tests of the control groups

The results of the loading tests of the different groups of control patients and healthy subjects are summarized in Table II. Two patients of group 3 (denoted C 1 and C 2 in Table I) reacted strongly to serine and also (although less dramatically) to glycine. None of the other patients reacted, though several patients felt tense and showed concomitant vegetative symptoms during loading days.

Two patients of group 2a, suffering from a temporal lobe epilepsy and a borderline state respectively, and a manic-depressive patient of group 3 were also loaded with double and triple doses of aminoacids, without result.

A patient suffering from residual schizophrenia and a hebephrenic patient were also loaded with L-alanine and L-methionine.
Vegetative symptoms were noted after methionine and no reactions after alanine.

The Incorrect Predictions

Thus, nine patients (group 1a) were incorrectly predicted. A retrospective and follow-up investigation made clear why six of these patients were erroneously included in group 1a (see Discussion).
Incorrect negative predictions occurred in two subjects from control group 3 (C 1 and C 2 in Table I).
Most errors in this respect were made during the first years of our study (1978/1979), also being the years during which the loadings of group 1a took place. Only one patient was wrongly predicted during the period 1980/1981.

TABLE II

CONTROL LOADING TESTS

Group	Number	Hospital diagnosis	Reported dysper-ceptions	Number of responsive patients
2a	1	minimal brain damage	+	0
2a	1	tryptophan malabsorption	+	0
2a	1	temporal lobe epilepsy	+	0
2a	1	LSD-abuse	+	0
2a	1	borderline state	+	0
2b	4	residual schizophrenia	+	0
3	2	hebephrenia	-	0
3	6	manic-depressive illness	-	0
3	5	atypical mania	-	1
3	6	psychogenic psychosis	-	1
3	4	hysterical psychosis	-	0
3	1	alcohol hallucinosis	-	0
4	15	healthy controls	-	0
Total	48*		Total	2

* mean age 27 year (range 17-45)

'Spontaneous' loadings by food-stuffs

A 'natural' loading was observed in patients nr. P 1 and P 5. The first patient became psychotic twice after eating herring and french frieds with mayonaise, the other patient after having consumed a large quantity of peanuts. Herrings and peanuts are rich in serine and glycine. (100 grams of herring contain 947 mg serine and 1062 mg glycine; 100 grams of peanuts 1460 and 1620 mg respectively).

DISCUSSION

The hypothesis that hallucinogenic substances can be rather simply synthesized endogenously by a faulty methylation of monoamines was proposed by Harley-Mason, Osmond and Smythies (10). The many similarities between hallucinogenic drug-induced states and some types of schizophrenic psychoses make this hypothesis attractive. Numerous efforts to prove this hypothesis have been published, varying from the detection of an abnormally methylated monoamine (3.4-dimethoxyphenylethylamine) in urine (11, 12), to experiments in which an excessive dose of a methyl-donor was administered to chronic schizophrenic patients in order to stimulate the assumed aberrant methylation (13). In this and later reports the methyldonor methionine was given daily for a prolonged period of time. Although a psychotic reaction did occur in several patients, the exact nature of the psychotic reaction was not clear. A toxic psychosis superimposed upon the residual schizophrenic state, but also the emergence of typical schizophrenic symptomatology could be observed in schizophrenics (14).

In most studies a MAO inhibitor was used. With administration of the methyl donor only, a reaction was reported in 40% of the patients (14). In a study of Antun glycine was used as a control aminoacid. Reactions were not seen (15).

Serine was not used in these experiments, although the role of serine as an ultimate source of carbon units was known at that time (16).

Only recently the possible role of serine in aberrant one carbon metabolism has been emphasized (17, 18). In vitro serine hydroxymethyltransferase (SHMT) is capable of forming tetrahydro-beta-carbolines from tryptamine (19).

There is evidence that these substances are psychoactive compounds in the mammalian body, and some of the derivatives found in plants are hallucinogenic compounds (20-24). The latter finding is of great interest in the light of our own experiments with patients.

It can be expected that an increased conversion of serine to glycine by the enzyme SHMT will occur during periods of excessive pyrrolsynthesis, as occurs in porphyria, and subsequently will increase the formation of N^5N^{10}-methylene tetrahydrofolate. This can result in an oversaturation of the normal folic acid-B_{12} pathway to homocysteine as the methyl accepter. It was postulated that under such circumstances the transport of one-carbon units could be shifted towards formaldehyde synthesis and excessive and possibly abnormal beta-carboline synthesis (1,5).

However, only two out of four patients proved to suffer from porphyria. This led us to extend the hypothesis to the notion that in all acute psychotic patients with

the characteristic symptoms, an excessive formation of N^5N^{10}-methylene tetrahydrofolic acid was responsible, due to a disturbance of serine-glycine metabolism. To demonstrate such a disturbance the patients who had recovered were orally loaded with serine, glycine or glucose (1).

To our surprise the characteristic symptoms were already evoked a few hours after one single loading of serine and/or glycine. Instead of glucose, L-alanine was administered to some patients, in order to exclude the possibility that a release of NH_3 was responsible for the reaction observed. No reaction could be observed. It is unlikely that the symptoms could be attributed to a NH_3 intoxication in view of the small quantities of NH_3 that will be synthesized from such a low dose and the capacity of the liver to convert ammonia to urea. Besides, the symptoms of NH_3 intoxication are different to those of a hallucinogenic drug-induced state.

The responsive patients

The patients who reacted to serine, glycine, or both, recognized almost immediately the changes and found them identical or similar to the changes experienced during, but especially at the onset of their psychosis. Some worried about the possibility of a full relapse.

As can be seen from Table 1, no uniform reaction pattern emerged for all patients. This is hardly surprising in the light of what is known about the different ways different personalities react to hallucinogenic drugs (25, 26).

Most patients did complain about sensory perceptual distortions, which is in complete agreement with out expectations.

In those patients who clearly showed a psychopathological reaction but without any reported distorted perception a placebo reaction should also be considered.

Two out of three patients not showing sensory perceptual distortions (no. P 9 and P 15) are known to be rigid, with very strong primitive ego defences such as denial of emotional and phantasy life, showing often psychosomatic reactions during stressful periods in their lives. Even during the loading test their attitude was garded, defensive, they were tense and both showed great resistance to acknowledge and report their reaction.

One patient (no. P 9), though admitting the very severe psychopathological changes (c.q. extreme depersonalization and motor inhibition) which occured during the loading, stated that it could not be true. A biological genesis of a mental illness did not fit in with her antipsychiatric oriented vision.

A change in attitude can also alter the experience of the reaction. This is well

illustrated by patient P 6, who at a first loading test at the age of 18 became depersonalised, paranoid and inhibited after serine, but reported no dysperceptions. At the time he was a childish boy, strongly emotionally attached to his mother, and had just started his university studies. He was very defensive regarding a discussion of his intrapersonal problems, which were evidently present. Two years later a second loading test was performed after his second psychotic episode. His personality had become much more mature and open, and he had become psychologically independent of his mother. The reaction to serine now gave different results (this reaction is rated in Table 1). Similar circumstances apply to patient P 16.
Patient P 4 reacted chiefly with euphoria and perceptual changes on serine in 1977, but reacted with distinct changes in time sense, body image and a negative mood in 1979 when serious individual and psychosocial problems were prominent.

In patients P 7, P 8, and C 2, only slight and perfunctory changes in sensory perception were reported. But in contrast to this the reaction as a whole was severe, with clearcut paranoid delusions and delusions of grandeur. Neuroleptic medication was considered, but finally it was decided not to interfere. No relation between the severeness of the natural psychotic episodes and the aminoacid-induced psychosis has been found, except for patient no. C 2 who has been hospitalized many times due to her frequent relapses.

Of considerable interest again are subjects C 1 and C 2, who were not predicted to react. During their natural psychotic states the dysperceptions were so inconspicuous that even during the post-psychotic interview these patients were considered as 'negative'. However, after the loading test both patients realized that the same changes though very perfunctory had also been present during their spontanous psychotic states.

Methionine as a methyl donor might also be able to evoke a reaction. However, administration of this aminoacid to serine reactive patients did not evoke specific symptoms.
It is not inconceivable that administration of serine and glycine over a prolonged period of time, comparable with the methionine loading test in schizophrenic patients, can induce mental alterations in more subjects. At least, the latter procedure might finally result in a decrease in concentration of brain aminoacids and diminuation in concentration of the neurotransmitters gamma aminobutyric acid, dopamine, and noradrenaline (27).

Organic factors and loading test

Among the 'reactive' patients there are some (P 2, P 4) with a known organic disease thought to be related to the disturbed serine-glycine metabolism. The relationship of this disturbed metabolism and porphyrin biosynthesis has been discussed elsewhere (1, 5), but two other patients (P 12 and P 18) need further explanation.

Patient P 18 has suffered from a chronic B-viral hepatitis since 1976, which has been treated with Prednison 10 mg and Azathioprine 50 mg daily since 1977. Following this he began to suffer from depressive episodes and later on from characteristic attacks in which he was extremely anxious and aggressive, accompanied by multiple sensory perceptual distortions and colourful hallucinations and finally a troubled sensorium. Although the attacks did not last more than 6 hours, the frequency of up to once a week caused great problems.

Folic acid therapy (15 mg/day) was prescribed despite normal blood levels. After 4 weeks of therapy attacks ceased. The loading tests performed were positive for glycine.

Patient P 12 had experienced 4 psychotic episodes, each lasting several months, during which the typical sensory distortions with an unimpaired consciousness were reported, in addition to delirious periods suggestive of an organic disease. Several liver function tests (transaminases) were intermittently disturbed together with a rise in body temperature. No cause has been found up to now.

The loading test procedure was repeated and both tests were positive for serine. During a later spontaneous psychotic episode, distinct epileptic discharges of temporal lobe origin have been found.

It is possible that the liver disease and/or its treatment of P 12 and P 18 may also have affected folate metabolism. The LSD-like symptoms that have been reported in a case of hepatic failure is of interest in this respect (28).

The fact that methyl tetrahydrofolate is an epileptogenic substance (29, 30) is of considerable importance in linking the various conditions: liver disease - special types of psychoses - epileptic phenomena.

In relation to the latter phenomenon it should be pointed out that our first patient also suffered from an epileptic attack during a psychotic episode, as did patient P 2, suffering from porphyria variegata, during a second admission. Patient P 8 showed an electro-encephalographic discharge pattern of temporal lobe origin. The so-called temporal lobe features of temporal lobe epilepsy are indistinguishable from many of the typical symptoms of the psychosis presently described, which may point to a common neurophysiological substrate. In this

context, it is worth noting that Mitsuda reports the frequent incidence of epilepsy in relatives of patients suffering from 'atypical' psychosis (31). This type of psychosis is probably identical with the so-called degeneration psychosis as diagnosed in our clinic (9).

The erroneous predictions

For three out of nine patients who did not show the expected response on the loading test, no obvious clue for this failure could be found.
One elderly patient (age 63 years) had suffered acute attacks of porphyria variegata with the characteristic psychotic symptomatology. The second patient had an anxious reaction with accompanying vegetative symptoms to all powders administered. The third patient reacted clearly only after glucose (see Results).
Of the other six patients it became clear that the diagnoses had to be revised: into hysterical psychosis twice, into reactive psychosis, manic-depressive psychosis and borderline state once; a schizophrenic process had to be diagnosed in one patient.
The observation period after the negative loading tests made clear that the latter patient became more and more withdrawn, lived in a bizarre delusional world and finally inappropriate affect and affective blunting became evident.

The remaining five patients have some characteristics in common that have led to the faulty prediction. These patients suffered from a subjective intensification of light and sounds. One patient could not bear this without ear props and sunglasses. After the negative loading results it was realized that none of these patients suffered from anomalous perception of colours, nor did they complain about a distorted perception of shapes, distances etc. Thus a more general oversensitivity rather than a distorted perception was present.
All patients also suffered from severe depersonalization. It is apparently the same subjective intolerance to bright light, noises etc. as encountered in the neurasthenic syndromes, which can also exhibit depersonalization (32).
In addition, two out of these five patients also said that they intermittently suffered from a distorted perception of the faces of others or of their own mirrored faces. Inquiry made clear that these distortions were indeed very selective, as the rest of the surroundings were perceived as unchanged. It is conceivable that these isolated dysperceptions can be understood as being comparable with conversion reactions such as narrowing of the visual fields, micropsia, visual blurring etc.

Thus in retrospect it appears that two mistakes can be made.
Firstly, oversensitivity to light and sounds is very easily confused with the intensification and distortion of sounds and light as experienced by the positive patients.
Secondly, the presence of selective perceptual distortion can easily lead to an erroneous inclusion for loading. The distorted sensory perception during the psychosis of the reactive patients affects in principle everything that is perceived. It has a more global character, including dysperception of colours.

Control subjects

Healthy volunteers did not show any reaction. In the control patients with sensory perceptual disturbances belonging to another category of psychotic disorders no psychopathological changes were evoked. The negative reactions in the schizophrenic group do not exclude that dysmethylation of monoamines may be a possible cause of certain types of schizophrenic illnesses. Higher doses or administration for a longer period of serine or glycine may lead to psychopathological reactions.
Of the control groups of acute psychotic illnesses with a benign course but not showing disturbances in sensory perception, two patients reacted unequivocally on both aminoacids. Before loading their dysperceptions obviously had escaped attention (see Reactive Patients).
In the complete control group (all patients plus normals) minor reactions due to anxious anticipation have been observed less frequently than in the reactive groups. Conceivably, an inevitably more relaxed attitude of the persons observing may have contributed to this.

CONCLUDING REMARKS

Up to now the loading test as performed in our clinic seems a valuable device in constructing a homogenous group of patients out of the group of Unclassifiable Psychotic Disorders.
The postulated endogenous synthesis of hallucinogenic substances as a result of a disturbed serine-glycine metabolism, has still to be substantiated. The characteristic symptoms during the natural psychosis as well as most of the symptoms observed during the loading tests justify this hypothesis.
From a retrospective study (submitted for publication) we calculated that the annual incidence of new admissisons of this type of psychosis would be

2-3 patients out of 200 psychotics in our clinic. The detection of the patients during their first admission to our hospital did not exceed this number. The other patients were already known or have been referred to us.
During the study five patients, one of them suffering from variegate porphyria, refused the loading test procedures. Another patient died due to somatic complications. This patient suffered from acute intermittent porphyria.

ABSTRACT

In accordance with the transmethylation hypothesis we postulated that acute psychotic states showing complete recovery and characterized by a distorted sensory perception at the onset of the psychosis, are the result of an aberrant one-carbon transfer due to a disturbance in the serine-glycine metabolism.
After recovery from the acute psychosis a single oral loading with serine and in a few cases with glycine or serine as well as glycine evoked characteristic symptoms (chiefly changes in sensory perception and mood) in 22 out of 31 patients. Two patients in the control group reacted in an identical way. The symptoms started a few hours after administration of the aminoacid and lasted for several hours.
The psychoses of the reactive patients are a sub-group of the Psychotic Disorders Not Elsewhere Classified of the DSM-III. The simple loading tests described should be of great value in creating a homogenous group of psychotic disorders within the poorly defined group of the Unclassifiable Psychoses, and open a potentially rewarding path to increase our understanding of the biological basis of these psychoses.

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ADDENDUM OF 2 CASE REPORTS

Patient P 6, male; aged 21. Report of his second psychotic episode after a two year episode of uncomplicated life.

Psychosis broke out after a period of heavy physical training combined with a slimming diet in order to lose weight for a rowing competition. The night and the day following the (lost) competition were celebrated with a large quantity of alcoholic beverages and complete lack of sleep. Odd behaviour was observed the next day and (re)admission in our hospital was arranged.

Patient was anxious, had a reddened face and perspired profusely. He uttered short sentences, that held no relationship to each other. Nevertheless, it became clear that patient experienced the time as running very fast in contrast to his slowed train of thought. Occasionally time stood still.

Although the patient tried to tell us about his manifold sensations, he was unable to verbalize the rich visual dream-like experiences most of the time. Terrifying scenes like drowning and hanging were present, but almost every stimulus from the outer world evoked abundant visual imagery. Some questions made him panic, for he was unable to take phrases at an abstract level, but instead visualized and took them literally and concretely.

Frank hallucinations were also present, he saw the first author, to whom he ascribed magical powers (!), coming through closed doors and conversing with him.

The patient stated that he disliked the idea of being elected to be Jesus, however, he 'had the Cross', pointing to his crotch (the Dutch 'kruis' has both meanings), and simultaneously complained about pain in his left shoulder due to bearing the Cross. Many objects were thought to be related to the Holy Trinity (three billiard balls, three portions of food etc.).

Patient had floating sensations, saw everything deformed; colours, light and sounds were perceived as sharp, piercing, shrill and brilliant. Objects and his own body expanded and shrank constantly. He did not feel the overheated water on his skin when showering; fortunately the nursing staff were able to prevent him from burning himself severely. Patient also felt that some force was stretching him and that he was inflated. Moreover, others could look into his skull and thus know his thoughts. He deferred shaving, because he could shave his thoughts away from his head. He refused to look into mirrors for his gaze would destroy him. When eating he said that he could hear as well as taste the flavour of fruits.

Apart from a few short stuporous episodes, motor behaviour was strikingly less disturbed.

These dramatic and kaleidoscopic experiences disappeared after a few weeks during treatment with neuroleptics, a high calorie diet and appropriate separation. Although the perceptual disturbances were reported to be absent, the patient was nevertheless unable to concentrate and reacted on every stimulus. Short episodes of hallucinations and relative inability of abstract thinking remained present for a months. In this period patient often felt in a state of extreme blessedness, contrasting to the anxious episode at the onset of the psychosis. A systematic delusional system never emerged.

Loading test (positive for serine):
Three hours after administration of the powder it was noted that patient looked tense, was sweating and had a reddened face. He stated that he felt himself bodily slowed down and strangely empty. He reported that he was thinking very fast and felt more powerful, able to do anything.
He gradually became euphoric, but two hours later he reported that he perceived his surroundings as 'through the frame of a picture tube'. In addition, the frame was somewhat overturned. The centre of his narrowed field of vision was very clear, the outer area very dark. The brigthness of light and colours was dulled. Instead of his initial euphoric mood he became more and more withdrawn and suspicious. He walked slowly and very carefully and stated that time had slowed down too.
Eight hours after administration patient reported that he felt normal again. He attributed his suspicious attitude to the fact that the evoked mental and perceptual alterations reminded him of the onset of his natural psychosis which made him apprehensive and paranoid towards the investigator.

Patient P 11, 24-year-old female, became psychotic while on holiday, during which attempts to seduce her by a homosexual girlfriend mobilized old and repressed problems of sexual identity. Long nightly discussions without sufficient sleep followed till one day, at dawn, she noted that the otherwise colourful, brilliant landscape was completely colourless ('as if I was colour-blind'). From then she became more anxious and depressed, and after a few days, however, loss of sexual inhibition and motoric restlessness were noted. Loose verbal associations and the feeling that she possessed extraordinary powers were prominent on admission. In contrast to her first experience she stated that colours and sounds were very intense and that time was running fast. Objects and space were

deformed. She smelled blood and suffered from visual (fire) and auditive (words) hallucinations.
The patient herself was much more preoccupied with strange bodily feelings then with the changed environment or hallucinations. She complained about the feeling of being filled-up, pains all over and the feeling of electricity flowing into her body. Sometimes she felt herself shrinking and was terrified by the delusional belief of being changed into a boy. In addition, she stated that she could diffuse with others, although her capacity of thought reading was more often uttered.
She felt Jesus in her body, which held also some relationship to the fact that she thought she was able to make her sister pregnant. The condensation of the Dutch 'je zus' (= your sister) produced the evidence.
Although anxiety dominated, inexplicable feelings of ecstasy and unmediated direct apprehension of the 'essence of the universe' were sometimes present. Delusional ideas were restricted mostly to her problems of sexual identity, but even these were fleeting. Also transistory paranoid delusions and ideas of reference were present in addition to her tendency to attribute assessory supranatural transcendent meaning to every event and object.
Recovery took place gradually, with short relapses, but nevertheless complete within four months.

The spontaneous written account of her experiences after the loading day (positive for serine) is given here:
'About 11 o'clock I felt dizzy and had a stomach ache. The light outside pricked into my eyes and seemed unusually sharp.
I felt peaceful, but estranged from the surroundings. Objects were being deformed and shapes changed. Colours became very beautiful. I felt unreal and looked at others from a great distance. I had the sensation of being high from hashish.
Gradually I felt sicker, a sort of lump in my throat, my eyes were painful through a sort of pressure from behind them. I lay down with a scarf over my eyes, because the light even with my eyes closed was still piercing. The air pressed heavily upon me and felt woolly. Thinking centred upon round forms, the undulating floor. I felt that I grew longer, a stretching of head and feet. There was a burning sensation, above my nose, the thought of 'a third eye' flashed through me. Walking was very slow or seemed to be slow, my legs felt like spaghetti, weak, powerless.
The shining sun through the window made me think: 'It shines for me, it shines

due to me' (I recognized this from the first period of my admission). Thanks to the preserved sense of reality I succeeded to put it into normal proportions'.

CHAPTER V

DISCUSSION

In the first chapter a young woman is presented whose acute psychotic episode(s) were characterized by multiple distortions of sensory perception, while consciousness remained unimpaired. The resemblance with a LSD or mescaline drug-induced state was striking.
We postulated that endogenous production of hallucinogenic substances was responsible for her psychosis.

Metabolic aspects and loading tests

Based on literature, we conclude that such hallucinogenic substances can result from an increased production of one-carbon moieties. At the oxidation level of formaldehyde, non-enzymatic reactions with monoamines will result in the production of beta-carbolines or isoquinolines, several of which are potent hallucinogenics.
One-carbon metabolism is normally accurately tuned to the requirements of the ultimate methyldonor in almost all methylating processes: S-adenosylmethionine. When needed, the demethylation of serine, yielding glycine, is a source of de novo produced one-carbon units (in the form of N^5-N^{10} methylene THF).
A few metabolic pathways offer the possibility of a (temporarily) abnormal increased production of CH_2=THF and thus the enhanced risk of splitting into formaldehyde.
An increased pyrrol synthesis, as occurs in the acute porphyrias, in which an excess of the precursor glycine is needed, makes an increased serine to glycine conversion necessary.
Abnormally enhanced catabolism of glycine via the cleavage enzyme and in particular the succinate-glycine cycle is another possibility. However, such disturbances in metabolism of glycine are unknown.
Other metabolic diseases, genetic enzyme deficiences and vitamin deficiences

interfering with one-carbon metabolism are not likely to result in trapping of CH_2=THF due to complex feedback regulations.

A porphyric disease could be substantiated in 5 of our patients suffering from the characteristic psychotic states. One patient suffered from acute intermittent porphyria, and died during a porphyric attack. Another patient suffering from porphyria variegata refused the loading tests. Of the remaining two patients with porphyria variegata one reacted to the serine loading (patient P 2) and, remarkably, no response was observed in the other patient.
It is noteworthy that the porphyric disease of these latter four patients was discovered due to the current project. In these patients neurological, abdominal and dermatological features were absent or had been present rather inconspicuously before the actual psychosis.
Patient P 4 suffers from porphyria cutanea tarda which is related to the use of contraceptives and abuse of alcoholic beverages. The positive serine loading test in this patient offers an explanation for the psychosis observed, but complicates the understanding of the incompletely understood pathogenesis of porphyria cutanea tarda.

From a clinical point of view, the illness of the first patient corroborates the tentative diagnosis of AIP. However, this could not be proved biochemically.

In the much quoted study of Roth (see chapter I) a multiform psychosis accompanied by symptoms suggestive of porphyria has been described. However, the argument relating both conditions is refuted by the negative biochemical findings. A problem that is solved by Roth by introducing the term 'porphyria without porphynuria'.
The relationship between florid psychoses with concomitant somatic symptoms and a porphyric disease may even be of historical importance. King George III's multiform psychotic episodes have been attributed to porphyria (1), although this has been challenged by authorities in the field of porphyria variegata on biochemical and genetic grounds (2).
Regrettably, in the psychoses due to true or 'para' porphyria no unequivocal mention has been made of the typical distorted sensory perception we noted in our patients.

A disturbed serine-glycine metabolism could be demonstrated indirectly in most of the selected patients, whether suffering from porphyria or not. Serine evoked

characteristic psychopathological symptoms, identical with those reported during the natural psychosis, a few hours after loading with a low dose (2 mmol/kg body wt.), which is in agreement with the notion that an increased serine to glycine conversion is causally related to the described psychotic states in these patients.
In addition glycine, and both aminoacids (in a few patients) evoked characteristic symptoms. In these patients, this points to an elevated catabolism of glycine by the cleavage enzyme or the succinate-glycine cycle yielding one-carbon units too. More direct evidence for an increased serine to glycine conversion during the psychoses is offered by the low serine excretion in the first 4 patients, suggesting a high consumption. The elevated excretion of glycine of the first patient during psychosis is enigmatic. At least in this particular patient it is an argument against an increased catabolism of glycine or a reconversion of glycine to serine. The latter is in agreement with the findings of Richards and Scott (3), who demonstrated this impaired conversion in AIP patients.
According to the report three English AIP patients, at the moment free of symptoms, were orally loaded with glycine (25 mg). Serine and glycine plasma concentration was studied by hourly plasma sampling, after which a second loading dose of 25 mg was administered without plasma samplings.
No serine synthesis could be detected in these three patients. Remarkably, in the same study three Swedish AIP patients showed an increase in serine plasma concentration after loading within the same range as healthy controls.
No reason for this difference is given, nor do the authors allude to any other difference than the countries of origin.
It obviously escaped their attention, that, according to their own report, the Swedish patients were treated with vitamin B_{12}. The latter substance will facilitate normal methylation, or at least will discharge the methyl(ene) over-loaded THF-cobalamine cycles and thereupon deblock the inhibition of SHMT, making serine synthesis after glycine feeding possible again.
The temporarily beneficial effect of vitamin B_{12} administration in our first patients is in agreement with this.
Demonstrating a disturbed serine-glycine metabolism in the patients by means of estimations of the hourly serine and glycine plasma concentration during a loading test appears to be rather successful. The preliminary data suggest that serine steady state levels in serine positive patients are decreased without changes in concentration of other aminoacids. Besides glycine disappearance is delayed in serine reactive patients. Conversion of glycine to serine was impaired, while conversion of serine to glycine is enhanced (publication in preparation).
Before any definite conclusion can be drawn more patients have to be studied.

We were unable to collect 24 hour urine specimens in most of the patients during psychosis, due to lack of compliance.

As mentioned in Chapter I much attention has been paid to the methionine loadings of patients suffering from chronic schizophrenia. The intention of these experiments is the same as the present investigation, viz. to substantiate clinically a disturbed one-carbon metabolism supposed to be responsible for certain psychotic states.
(In the sixties, faulty transmethylation of catecholamines or indolamines was postulated to occur in 'schizophrenia', while in our hypothesis the cyclization of monoamines (most likely indolamines) is suggested to be causally related to well-defined acute psychotic states).

The earlier methionine loading tests were also quite successful in inducing new symptoms or flare-ups of psychotic symptoms in schizophrenic patients.
From the thorough review by Cohen (See Chapter I) it appears that at least 62 out of 107 patients (from 10 studies) reacted in some way to loading, whether or not MAO inhibitors were given concomitantly.
The nature of the reaction as an exacerbation of the already existing schizophrenic process has been doubted, since many of the descriptions are clearly suggestive of a superimposed toxic psychotic state.
Nevertheless, worsening of the pre-existing psychoses without organic signs has been reported in 32.7% of the patients studied. However, the idea that such a methionine loading will stimulate normal or abnormal transmethylation of catecholamines in man and animal has not been substantiated biochemically up till now (4, 5, 6, 7).
The essence of the reaction of the methionine loadings remains enigmatic, a disturbance in transsulfuration or indirect disturbance of monoamine metabolism instead of transmethylation may be responsible.
The limited number of methionine loading tests performed in healthy controls (5?) and in non-schizophrenic psychotic patients makes further speculation about the specificity of the reaction difficult.
The abundant literature on the presence of abnormally methylated derivatives of monoamines in urine of schizophrenics does not give solid proof for the transmethylation hypothesis. Discussion of these often conflicting results is beyond the scope of our present investigation.

It is doubtful if the 'hallucinogenic model of schizophrenia' is appropriate for all

schizophrenic psychoses. Sensory perceptual distortions are noted to occur only in some of the schizophrenic patients during the acute phase and nuclear symptoms of schizophrenia such as affective blunting, lack of insight and the preponderance of auditory hallucinations etc. are not found to be characteristic of hallucinogenic drug-induced psychotic states.
The latter arguments may be challenged by pointing out that there is insufficient information about chronic (daily for months) hallucinogen abuse, and thus does not allow a complete refutation of the transmethylation model of schizophrenia. More so-called schizophrenic patients who (have) suffer(ed) from dysperceptions ought to be examined.
At this moment only four residual schizophrenic patients, having suffered from dysperceptions, have been loaded in our series with negative result.
The natural psychosis of the respondent patients of the present study are much more concordant with a hallucinogenic model of psychotic illness. The natural type of psychosis observed and the emergence of unambiguous characteristic symptoms a few hours after loading in most of the recovered patients are completely compatible with such a model, even when one wishes to omit those induced reactions without the typical sensory perceptual disturbances of light, colours, sounds, shapes and distances (P 9, P 15, P 20).
The negative loading tests in other groups of psychotic illnesses stress the specificity of the reaction and make it a valuable instrument for defining a homogenous group of psychotic illnesses.

The (reported) absence of dysperceptions during a loading day may be due to personality or situational factors (see Chapter 4). Besides, the dose - 2 mmol/kg body wt. - may be too low to induce a full-blown reaction, but sufficient to provoke the early stages of the reaction (e.g. depersonalization). It can also not be excluded that a reaction can be restricted to vegetative symptoms and some feelings of apprehension or tension. Further experiments with higher and/or repeated doses are needed to clarify this. However, it seems more appropriate to use less burdening procedures (for the patient) such as the search for hallucinogenic substances in blood and urine.
The loading procedure as described is rather simple and not harmful to the patient. Administration of serine or glycine for weeks or months, similar to the methionine loadings, in order to evoke a reaction does not seem justified and possible late reactions during such a situation could be either specific or nonspecific toxic since the metabolic consequences of such a continuous amino-acid overload are not known.

Dietary / therapeutic factors

The literature provides evidence that catabolic states, e.g., starvation, post-operative conditions, slimming diets with a limited protein supply, will stimulate the serine-glycine metabolism in order to meet the demands for de novo methyl group and glycine synthesis.

The case histories of the patients show that such catabolic states are related to the outbreak of the psychosis, whether the patients concerned are suffering from porphyria or not. Moreover, there is preliminary evidence that the carbohydrate rich diet is also effective in patients not suffering from a porphyric disease. A follow-up study of several patients supports this idea, but definite conclusions cannot be drawn yet, as a larger number of patients will have to be studied for longer periods.

The beneficial 'glucose effect' in porphyria patients due to inhibition of the ALA synthetase, does not necessarily explain the effect in other non-porphyric patients, unless abnormal activity of the succinate-glycine cycle is responsible for the psychotic states. This route (the Shemin cycle) converts ALA into succinate, thereby converting glycine into CO_2,NH_3 and formaldehyde (!) (8). Inhibition of the ALA synthase will also diminish activity of this biochemical cycle. However, a general catabolite repression and the supply of exogenous labile methyl groups can be postulated to be responsible for the beneficial effects as well.

Changes in the transport of precursor substances as tyrosine and tryptophan, and methionine, serine and glycine itself by the carbohydrate rich and fat deficient diet, complicate a simple understanding of the dietary influences (9, 10).

With regard to therapeutic measures there is the problem of neuroleptics remaining ineffective, a clinical impression which is difficult to substantiate. Retrospective study and daily practice give the impression that in most patients the course of the disease is not or barely influenced by these drugs. It should be noted that such a failure in coping with psychotic symptoms has been noted and demonstrated in schizophrenia-like emotional (11) and schizoaffective psychoses (12). Nevertheless, the sedating effects of neuroleptics are useful in the management of these patients. The observations fit rather well the idea that in these psychoses the dopaminergic system is not responsible for the psychotic symptoms as is assumed for schizophrenic psychoses.

The therapeutic and preventive effects of lithium in this type of psychosis also needs to be studied extensively. No definite conclusions can be drawn from the few patients who were treated with lithium. The lithium administration at least

did not prevent aminoacid-induced mental alterations.
Lithium may influence methyl group metabolism, since it has been demonstrated that red blood cell concentration of choline and glycine is increased during lithium administration (13, 14).
The clinical effects of valproate may be of interest too, because of the reported inhibitory effect on the glycine cleavage enzyme (15).

Clinical aspects

The clinical picture the first patient showed after the operation imitated a LSD or mescaline induced state to such an extent that an intensive search and inquiry was undertaken to demonstrate a possible abuse of such substances.
Her case history, however, lead us to postulate an endogenous synthesis of hallucinogenic substances.
In the retrospective study only one patient (out of 27) was reportedly suspected of such a drug abuse based on the characteristic clinical picture.

Textbook descriptions emphasize the sensory perceptual distortions and psychedelic experiences of hallucinogenic use. The problems of prolonged administration and habituation, the influence of personality factors shaping the drug-induced, altered mental state, the incorporation of perceptual anomalies in new conceptions and notions that can conceal the original perceptual experiences etc. are neglected. What holds for exogenous hallucinogenics will also hold for such endogenous substances.
Thus, short-lived or even absent disturbances in sensory perception do not refute the hypothesis of endogenous synthesis of hallucinogenic substances in these patients. The positive loading tests in the two patients from the control group demonstrate how perfunctory experiences of altered sensory perception can escape the patients' attention, or how their memory may be blotted out by the subsequent psychotic experiences.

The problems of the clinical presentation of dysperceptions as reported by patients have been well understood and investigated by orthomolecular psychiatrists (16, 17).
The Experiential World Inventory of El-Meligi and Osmond in its present or a revised form may be of importance to unravel patients' experiences into fundamental categories (18, 19).

Classification

It was assumed that all psychotic episodes of the first patient were also caused by the postulated disturbance(s) in serine-glycine metabolism.
The most impressive change in the clinical picture observed on the ward took place when the akinetic hallucinatory drug-like state changed into the hyperkinetic-paranoid amphetamine-like psychosis.
It is tempting to speculate, regarding the effect of the addition of tryptophan to the diet, that a substantial depletion of the most likely substrate for abnormal one-carbon transfer, viz. the indolamines (20, 21) opened up the possibility for alternative routes of abnormal one-carbon transfer, in particular the catecholamines.
All sorts of psychotic states were observed previously: catatonic, depressive, hypomanic, auditive and visual hallucinosis-like episodes or mixtures of these.
When trying to reduce all these different psychoses to one common denominator, the vague label of schizoaffective psychoses seems most appropriate.
In agreement with the DSM-III the adjective 'unclassifiable' is completely justified, which in that context means that criteria for schizophrenic, paranoid, organic, and affective psychotic disorders are not fulfilled. The term Unclassifiable (literally: Psychotic Disorders Not Elsewhere Classified) denotes the doubt of American psychiatry in strict adherence to the two entity principle, whether a separate category of psychoses apart from the classically recognized functional psychoses can exist.
Such a point of view is in sharp contrast with the European (and Japanese) ideas. Cycloid, psychogenic, degeneration psychosis, bouffée delirante, are regarded as separate psychotic entities. Despite the fact that there is considerable overlap between the psychogenic psychoses on one hand and the cycloid, and degeneration, atypical psychoses, bouffée delirante on the other, and that in course of time a schizophrenic or manic-depressive illness may be recognized as the basic illness, the former psychoses are firmly rooted in European psychiatry.
Long before the schizoaffective psychosis was 'discovered', the label of degeneration psychosis was intended to designate exactly all those psychoses bearing resemblance to the functional psychoses, but showing their own clinical courses. They were also considered to be autochthonous (22, 23).
At present, at least in our clinic, and in agreement with its predecessor the 'bouffée delirante des degenerées' (!) of Magnan (22) the use of the term has become restricted to a characteristic type of acute psychoses, viz. psychosis in which the patient is overwhelmed by visionary, cosmic and ecstatic experiences,

delusional ideas, abundant hallucinations, ideas of grandeur, prophetic-ecstatic states, sudden insights, motor disturbances and strong lability of affects, with a tendency to show a complicated, polymorphous and alternating picture (25). (When euphoric mood accompanied by verbal and motor desinhibition dominate the clinical picture, the term atypical mania instead of degeneration psychosis is also used.)
These atypical manias/degeneration psychoses do differ from the reactive/ psychogenic psychoses from a descriptive point of view. The cycloid and atypical psychoses have more in common with the degeneration than with the psychogenic psychoses.

The retrospective study, solely based on the presence of dysperceptions, unexpectedly supported this twofold division regarding 'schizoaffective and related psychotic states' commonly made in our clinic.
The disturbances in sensory perception were found to be mostly associated with the diagnosis degeneration psychosis, whereas a lack of distorted sensory perception together with the presence of distinct depersonalization was noted in the psychogenic psychoses.
In some of the descriptions in case histories of cycloid, schizoaffective, and degeneration psychoses, dysperceptions are mentioned by their authors. In other words the model psychoses of LSD, mescaline, psilocybin do indeed exist in nature, however paradoxically this may sound.

In my opinion the overlooking or underestimation of this possibility must be due to the mostly very short-lived, and/or perfunctory experience of the dysperceptions. It was the longlasting presence of these disturbances in the first patient that made us aware of and evoked our interest in the possibility of endogenous synthesis of hallucinogenic substances.
From the present studies it is evident that short-lasting dysperceptions do not exclude such a synthesis.
From the failure to induce mental changes by aminoacid loadings in some patients it has become clear that when dysperceptions are present they have to be characterized by a global character, including changes of colour perception and of perception of the whole spatial world.
The experience of intensification of light and sounds, disturbed time sense, changes in body image and of distorted perception of single items are not pathognomonic by themselves, and have no predictive value with respect to a positive reaction after a serine or glycine loading.

Some types of psychoses also exhibit global dysperceptions and give difficult differential diagnostic problems.
Temporal lobe epilepsy, borderline states, acute schizophrenic psychoses have to be excluded. EEG and follow-up studies are necessary to disentangle these problems. And in general all organic processes which may interfere with the neurophysiological systems involved in perception, must be reviewed on negative loading tests. After positive loading tests, porphyria must be excluded.
The exact nature of the aberrant serine-glycine metabolism in the remaining patients will have to be established. However, for the time being, the relatively simple loading test offers the possibility of distinguishing one type of psychosis from the large group of acute psychotic illnesses. The test also shows that this type of psychosis can be recognized most of the time without great difficulty by the presence of characteristic global dysperceptions.

These phenomenological and biochemically-induced characterizations enable us to reclassify the 'Psychotic Disorders Not Elsewhere Classified'. It appears that former claims from European and Japanese psychiatry regarding classification of acute psychotic states with complete recovery but a tendency to run an episodic course, cannot be simply ignored by assuming that they are all and the same, merely schizoaffective.
The present studies emphasize that typological descriptions of the degeneration or atypical psychoses versus reactive/psychogenic psychoses are of considerable importance for nosological purposes. However, the simple classification offered here on basis of a few pathognomonic clinical characteristics and a biochemically inducable reaction will be of value in attempts to prove that a third functional psychosis does exist.
Further biochemical studies to unravel the nature of the disturbed serine-glycine metabolism, and to demonstrate the synthesis of a hallucinogenic substance caused by it, are in progress.
Follow-up and family studies and the ongoing studies of the effect of dietary measures are necessary to confirm the entity of the episodic polymorphous psychoses (26).
Moreover these studies should result in improved treatment and prevention of these psychotic states.

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SUMMARY

This thesis comprises an investigation into the clinical-phenomenological aspects and the experimental-biochemical determination of a subtype of acute psychoses. Psychoses which in general show complete recovery, mostly have an episodic course and belong to the large group of acute psychotic syndromes which cannot be classified either as manic-depressive, schizophrenic, paranoic, or as organic.

In chapter I there is the case history of a patient suffering from acute psychotic eposides. After an operation she showed a psychosis identical with a LSD- or mescaline-induced state. Acute intermittent porphyria might be the cause of the psychosis. A high carbohydrate diet resulted in complete recovery.
It was assumed that as a result of increased porphyrin production, hallucinogenic substances are synthesised.
The enlarged porphyrine synthesis makes an increased conversion of serine into glycine - one of the precursor substances of porphyrins - necessary. Methyl tetrahydrofolate being disengaged in the process of serine into glycine conversion will accumulate, augmenting the chance of segregation of formaldehyde.
A non-enzymatic reaction of formaldehyde with monoamines will result in the production of psychotogenic substances of the beta-carboline and isoquinoline type.

An investigation into the literature on the incidence of such psychotic syndromes in porphyria and also in metabolic diseases and vitamin deficiencies, often supposed to create an accumulation of active carbon moieties such as methylene- and methyl-tetrahydrofolate, turns out to be negative.
The biochemical literature appears also to offer few cues to postulate that vitamin B_{12} deficiency and homocystinurias a.o. will cause a considerable accumulation of methylated folates. Only a forced catabolism of serine and glycine, in porphyria or otherwise, seems to make this possible as things stand now.

In chapter II four patients are described in short. All were suspected of suffering from porphyria and had been suffering from psychoses in which sensory disturbances of light, colour, sound, shape, space, and time were mentioned.
In two patients porphyria could be diagnosed, though a high carbohydrate, low fat and low protein diet resulted in quick recovery in all patients.
Based on the central thought that an accelerated conversion of serine into glycine should be the cause in all patients, oral loadings of serine, glycine, and glucose in restricted quantities (2 mmol/kg bodyweight) were attempted. The investigation was carried out double blind.
Some hours after administration, all patients reacted to serine with distinctive phenomena; the first patient was also reactive to glycine.
In particular depersonalisation, changes of mood and characteristic perceptual disturbances were induced.
It is concluded that a disturbance in serine and glycine metabolism is the cause of the psychoses.

In chapter III it becomes clear by means of a retrospective investigation of 71 case histories that acute psychoses characterized by dysperceptions have been regularly observed (n = 27). It appears that these perceptual anomalies are mainly mentioned at the onset of a psychosis.
It also appears that this type of psychosis generally shows a kaleidoscopic, polymorphic picture.
They are, on the strength of their clinical description, so-called 'degeneration psychoses'. They are clearly distinct from a second group of acute psychosis without dysperceptions: mostly diagnosed as psychogenic psychoses, in which the clinical picture is determined by strong depersonalisation (n = 35).
This approach offers a completely new classification of the so-called Unclassifiable Psychoses of the DSM III.

In chapter IV the results of the loading tests with serine, glycine, glucose and occasionally with alanine and methionine are discussed.
Out of a total number of 31 patients who were expected to react on account of their clinical picture - which should be characterized by dysperceptions - 22 patients turned out to show the expected response to serine, glycine or both amino acids.
Of six patients an erroneous diagnosis (schizophrenia a.o.) and/or confusion regarding the character of the dysperceptions appears to be the cause of the wrong predictions.

From the controlgroup (33 patients having suffered from other psychoses and 15 healthy subjects), 2 patients also turned out to react to serine and glycine. The dysperceptions of these two patients had been of such a short duration that they were not reported.
Conclusion: The reactions to serine and glycine appear to be highly specific for the described group of psychoses and support the hypothesis that endogenous synthesis of hallucinogenic substances may be the cause of these psychoses.

In chapter V the various results are integrated. The idea, already put forward at the beginning of this century, that the degeneration psychoses form the third group of the so-called functional psychoses, will get a renewed and biologically founded base by the improved clinical and new experimental diagnostics as described in this thesis.

SAMENVATTING

Dit proefschrift beschrijft een onderzoek naar de klinisch-fenomenologische aspecten en de experimenteel-biochemische determinatie van een subgroep van acute psychosen. Psychosen die in het algemeen restloos herstellen, veelal episodisch verlopen en behoren tot de grote groep van acute psychotische syndromen die noch als manisch-depressief, schizofreen, paranoïd of als organisch kunnen worden geclassificeerd.

In het eerste hoofdstuk wordt een patiënte beschreven, lijdende aan acuut optredende psychotische episoden. Na een operatie vertoonde zij een psychose, identiek met een LSD of mescaline geïnduceerde toestand. Een acute intermitterende porfyrie zou mogelijk de oorzaak van deze psychose kunnen zijn. Een koolhydraatrijk dieet bracht volledig herstel.
Hierbij werd verondersteld, dat, als gevolg van de verhoogde porfyrine-aanmaak, hallucinogene stoffen worden gesynthetiseerd. De toegenomen porfyrinesynthese maakt namelijk een verhoogde omzetting van serine in glycine - één der precursor-substanties voor porfyrines - noodzakelijk. Het bij de serine-glycine-omzetting tegelijkertijd ontstane methyleen-tetrahydrofolaat zal zich ophopen, waardoor de kans op afsplitsing van formaldehyde toeneemt. Een non-enzymatische reactie van formaldehyde met monoaminen resulteert in de produktie van psychotogene stoffen zoals beta-carbolinen en isoquinolinen.

Een literatuuronderzoek naar het vóórkomen van dergelijke psychotische syndromen bij porfyrie alsmede bij stofwisselingsziekten en vitamine-deficiënties, waarvan veelal verondersteld wordt dat zij ophoping van actieve koolstofeenheden (onder andere methyleen- en methyl-tetrahydrofolaat) zullen geven, viel negatief uit.
Eveneens blijkt dat de biochemische literatuur weinig aanknopingspunten biedt door te veronderstellen dat onder andere vitamine B_{12}-deficiëntie en homocystinurieën een aanzienlijke ophoping van gemethyl(een)eerde folaten zullen veroorzaken. Alleen een geforceerd catabolisme van serine en glycine, al dan

niet gekoppeld aan porfyrie, lijkt dit vooralsnog mogelijk te maken.

In het tweede hoofdstuk worden in het kort vier patiënten beschreven. Allen werden verdacht te lijden aan porfyrie en hadden aan psychosen geleden, waarbij waarnemingsstoornissen van licht, kleur, geluid, vorm, ruimte en tijd werden vermeld. Bij twee patiënten kon een porfyrie worden vastgesteld, hoewel bij allen een koolhydraatrijk, vetarm, eiwit-beperkt dieet resulteerde in een snel herstel.
Vanuit de centrale gedachte dat een versnelde omzetting van serine in glycine bij alle patiënten de oorzaak zou moeten zijn van de psychose, werd overgegaan tot orale toediening van serine, glycine of glucose in een beperkte hoeveelheid (2 mmol/kg lichaamsgewicht). Het onderzoek werd dubbelblind uitgevoerd. Alle patiënten reageerden, enkele uren na inname, met kenmerkende verschijnselen op serine; de eerste patiënte bovendien ook nog op glycine. Met name werden depersonalisatie, stemmingsveranderingen en karakteristieke waarnemingsstoornissen geïnduceerd.
Conclusie: een stoornis in het serine- en glycine-metabolisme is waarschijnlijk de oorzaak van de psychosen.

In hoofdstuk III wordt door middel van een retrospectief onderzoek van 71 ziektegeschiedenissen duidelijk, dat acute psychosen, gekenmerkt door "dyspercepties", regelmatig geobserveerd zijn (n = 27). Het blijkt dat deze waarnemingsanomalieën vooral aan het begin van een psychose worden vermeld. Ook komt naar voren dat dit type psychose in het algemeen een kaleidoscopisch, polymorf beeld vertoont. Op basis van hun klinische descriptie zijn het zogenaamde "degeneratiepsychosen". Zij onderscheiden zich duidelijk van een tweede groep van acute psychosen zonder dyspercepties: meestal gediagnostiseerd als psychogene psychosen, waarbij sterke depersonalisatie het klinische beeld bepaalt (n = 35). Deze benadering biedt een geheel nieuwe classificatie van de zogenaamde Onclassificeerbare Psychosen van de DSM-III.

In hoofdstuk IV worden de resultaten van de loading tests met serine, glycine, glucose en in enkele gevallen met alanine of methionine besproken.
Van het totaal van 31 patiënten die verwacht werden te reageren naar aanleiding van hun klinisch beeld - dat gekenmerkt moest zijn door dyspercepties - bleken 22 patiënten de verwachte respons te vertonen op serine, glycine of beide aminozuren.
Bij 6 patiënten blijkt een foutieve diagnose (onder andere schizofrenie) en/of

verwarring omtrent de aard van de dyspercepties de oorzaak te zijn van de onjuiste predictie.
Uit de controlegroep (33 patiënten die aan andere psychosen hebben geleden en 15 gezonde proefpersonen) blijken 2 patiënten te reageren op serine en glycine. Bij deze twee patiënten waren de dyspercepties van zulk een korte duur geweest dat ze niet waren vermeld.
Conclusie: de reacties op serine en glycine blijken in hoge mate specifiek te zijn voor de beschreven groep psychosen en ondersteunen de hypothese dat endogene vorming van hallucinogene stoffen de oorzaak van deze psychosen kan zijn.

In hoofdstuk V worden de verschillende bevindingen geïntegreerd. Het reeds aan het begin van deze eeuw geponeerde idee dat de degeneratiepsychosen de derde groep van de zogenaamde functionele psychosen vormen, krijgt door de in dit proefschrift beschreven verbeterde klinische en de nieuwe experimentele diagnostiek een hernieuwde en biologisch gefundeerde basis.

ADDENDA

Enzymes and Neurotransmitters in Mental Disease
Edited by E. Usdin, T. L. Sourkes, and M. B. H. Youdim

ROLE OF SERINE, GLYCINE, AND THE TETRAHYDROFOLIC ACID CYCLE IN SCHIZOAFFECTIVE PSYCHOSIS. A HYPOTHESIS RELATING PORPHYRIN BIOSYNTHESIS AND TRANSMETHYLATION

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SCHIZOPHRENIA AND TRANSMETHYLATION

The resemblance between drug-induced hallucinations and schizophrenia has been the inspiration for many scientists in the search for endogenous toxic products responsible for psychotic symptoms in these patients. The isolation of potent hallucinogens from South American snuffs and the identification of these substances as derivatives of tryptamine, such as N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine (Holmstedt and Lindren, 1967), revived interest in the possibility that methylation of tryptamine or 5-hydroxytryptamine (5-HT-serotonin) respectively, (compounds formed *in vivo* from the amino acid L-tryptophan) represents a biochemical pathway involved in evoking psychotic symptoms. 5-Methoxytryptamine has been detected in rat brain tissue and at particularly high concentrations in the hypothalamus (Green *et al.*, 1973). It has been suggested that this compound might act as a precursor of the potent hallucinogen, 5-methoxy-N,N-dimethyltryptamine (Snyder *et al.*, 1974).

The formation of hallucinogenic substances from monoamines *in vivo* by a

faulty transmethylation reaction was postulated by Harley-Mason in 1952 (see Osmond and Smythies, 1952). However, until now no evidence has been provided for the formation of such methylated monoamines during psychosis. Although dimethyoxyphenylethylamine has been isolated from the urine of acute schizophrenic patients (Friedhoff and Van Winkle, 1962), a finding which has been confirmed by others, this compound has also been isolated from urine of individuals without psychiatric disorders (Watt *et al.*, 1969). The formation of methylated monoamines in psychotic patients is still a controversial issue, but the enzymes responsible for the formation of these substances have been reported to be present (see Rosengarten and Friedhoff, 1976). In 1961, Axelrod described an enzyme in rabbit lung which converts 5-HT and tryptamine into N,N-dimethylserotonin and N,N-dimenthyltryptamine, respectively. This enzyme also N-methylates phenylethylamines. This methyltransferase has also been detected in brain tissue (Saavedra and Axelrod, 1972; Saavedra *et al.*, 1973). Furthermore, the presence of a specific indole(ethyl)-amine N-methyltransferase has been reported in chick brain (Morgan and Mandell, 1969). Subsequently, This enzyme was also shown to be present in the brains of sheep and man (Mandell and Morgan, 1971).

These methyltransferases use S-adenosylmethionine (SAM) as a methyldonor. The report that an N-methyltransferase may convert dopamine into epinine, using N^5-methyltetrahydrofolic acid (N^5-methyl-FH_4) as a methyldonor (Laduron, 1972), renewed the search for transmethylations in which N^5-methyl-FH_4 would act as a more specific methyl donor. Banerjee and Snyder (1973) reported the presence in rat brain of a methyltransferase which not only N-methylates tryptamine derivatives as well as phenylethylamines, but which also methylates 5-HT to 5-methoxytryptamine using N^5-methyl-FH_4 as a substrate. However, Lin and Narasimhachari (1974) were not able to confirm this finding.

Soon afterwards it became clear that N,N-dimethyltryptamine was not the product formed from N-methyltryptamine and N^5-methyl-FH_4, but rather 2,3,4,9-tetrahydro-2-methyl-1H-pyrido (3,4b) indole, a tetrahydro-β-carboline, probably by oxidative cyclization (Mandel *et al.*, 1974). This reaction, however, did not occur when SAM was used as a methyl donor, suggesting the N^5-methyl-FH_4 might act as a more specific methyl donor. Subsequently, it was shown that epinine is not formed after incubation of dopamine and N^5-methyl-FH_4, but rather a tetrahydroisoquinoline (Meller *et al.*, 1975).

With regard to the formation of these newly discovered products, evidence has been presented that N^5-methyl-FH_4 is converted to N^5-methylene-FH_4 which is further degraded to formaldehyde. The latter product is responsible for the formation of isoquinolines or tetrahydro-β-carbolines from catecholamines or indoleamines, respectively (Meller *et al.*, 1975; Pearson and Turner, 1975).

A survey of the biochemical pathways involved in transmethylation is presented in Fig. 1. All the biochemical reactions in this figure occur in the liver as well as in the brain (see Gaitonde, 1970). As can be seen from Fig. 1, the initial step in one-carbon transfer is the conversion of serine to glycine which may exert a key function in the synthesis of N^5-methyl-FH_4,

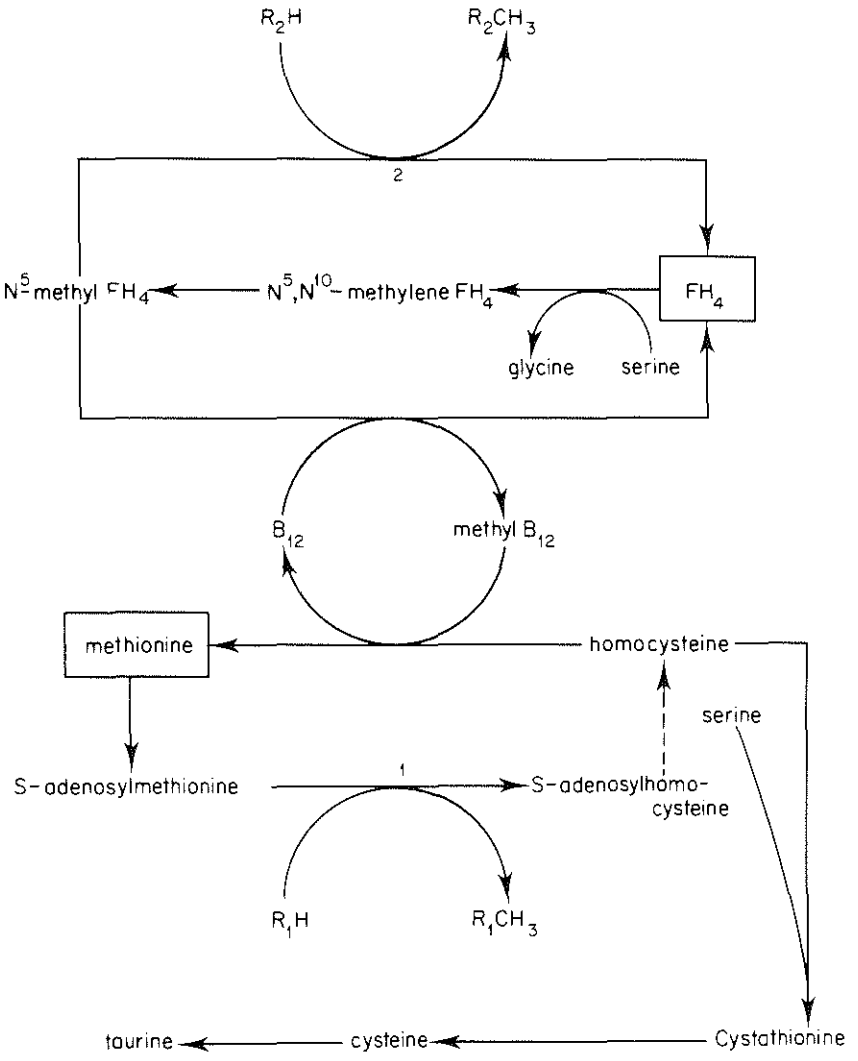

Fig. 1. Pathways involved in the biosynthesis of methylfolates and S-adenosylmethionine

N^5,N^{10}-methylene-FH_4 and of SAM. The first product formed in the conversion of serine to glycine is N^5,N^{10}-methylene-FH_4. This product is subsequently converted into N^5-methyl-FH_4 by methylenetetrahydrofolate reduc-

tase, an enzyme which is inhibited by SAM. S-Adenosylhomocysteine counteracts the inhibition of the reductase by SAM (Kutzbach and Stokstad, 1967, 1971).

Clinical evidence that the tetrahydrofolic acid cycle is involved in schizophrenia, or in psychosis in general, is not available (see Bruinvels, 1975). However, one patient has been described with homocystinuria and symptoms of schizophrenia (Freeman *et al.*, 1972; Mudd *et al.*, 1972) in which N^5,N^{10}-methylene tetrahydrofolate reductase activity was found to be impaired. It has also been reported that treatment of some epileptic patients with anticonvulsants, such as phenylhydantoin, may provoke symptoms which resemble schizophrenia. Reyonds *et al.* (1966) suggested that lowering of the folate level by anticonvulsant drugs might be responsible for the schizophrenia-like symptoms. Based on this suggestion, a hypothesis was put forward by Levi and Waxman (1975) relating methionine and folate metabolism to the pathogenesis of schizophrenia (see also Noris and Pratt, 1974).

SCHIZOAFFECTIVE PSYCHOSIS AND TRANSMETHYLATION

About two years ago a female patient was admitted to our psychiatric department who exhibited a clinical picture resembling a drug-induced psychosis. However, drug abuse could be excluded. The most distinct features of this patient were impressive perceptual disturbances, including perceptual distortions of the surroundings, brightness of light and colors, and changes in passing time. These characteristic features are also known to occur during the acute phase of schizophrenia. However, the course of the disease in this patient, e.g. its episodic character, with complete recovery—leaving no residual symptoms—after each psychotic period, the lack of thought disorder and a normal emotional responsiveness (even during a severe psychotic attack) excluded a schizophrenic process. In addition, treatment with neuroleptics was unsuccessful. When it was realized that during periods preceding the psychotic ailment depressive and/or manic symptoms had dominated the clinical picture, it was concluded that classification under the category of schizoaffective disorders would be more appropriate, at least from a diagnostic point of view.

After some months, this patient developed neurological complications which were suggestive of porphyria. At this point a neurologist decided to treat the patient with vitamin B_{12}, despite a normal plasma concentration of this vitamin. During the following week the neurological symptoms as well as the hallucinations disappeared. However, one of the nurses accidently gave the patient a sleeping pill containing, among other substances, a barbiturate which again induced porphyric symptoms and psychotic reactions, including

cataleptic episodes. These cataleptic episodes lasted from minutes to hours. Still under the convinction that the patient suffered from porphyric disease, high doses of glucose were administered, a therapy based on the inhibition by glucose of δ-aminolevulinate (ALA)-synthetase, the rate-limiting enzyme of porphyrin biosynthesis (Welland, 1964; Stein and Tschudy, 1970). Although no abnormal excretion of porphyrins could be detected, the patient recovered in two days. A diet rich in carbohydrates, low in protein and fat prevented further serious relapses. Breaking of this diet, when the patient ate herring or chips with mayonnaise, once again induced psychotic reactions with a 5–6 h delay. The psychotic period lasted only a few hours, unless further feeding was refused.

Hypothesis relating transmethylation and porphyrin biosynthesis

Based on the findings in this patient, a hypothesis relating psychosis and porphyrin biosynthesis was worked out. This hypothesis is presented in Fig. 2 and is in fact composed of two biological systems, one being the system involved in one-carbon transfer (Fig. 1) and the second system representing

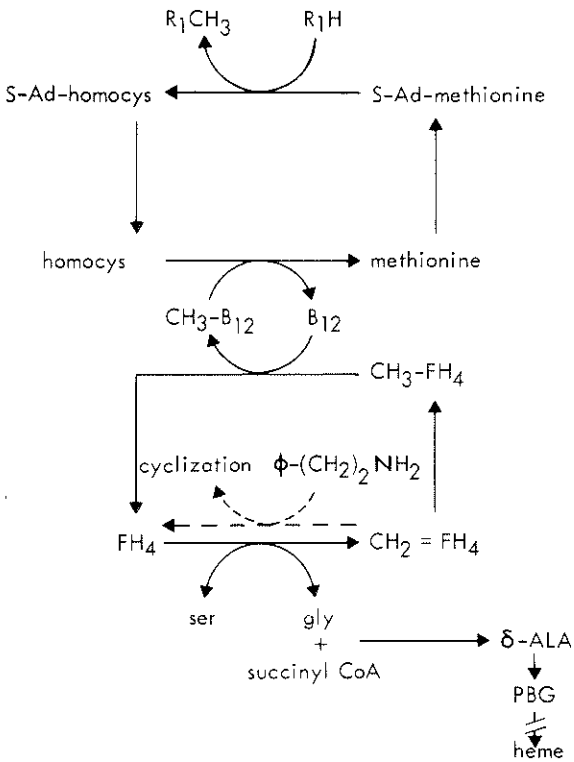

Fig. 2. Hypothesis relating porphyrin biosynthesis and transmethylation. Ad = adenosyl; PBG = porphobilinogen

porphyrin biosynthesis. Both systems are coupled by the serine–glycine conversion. In this latter system, a one-carbon unit of serine is transferred to tetrahydrofolic acid (FH_4) resulting in the formation of glycine, one of the substrates for the biosynthesis of porphyrin, and N^5,N^{10}-methylene-FH_4. During porphyria, more glycine needs to be made available and therefore, the conversion of serine to glycine will be increased under these circumstances. Since serine–glycine conversion is the main pathway for the synthesis of glycine, one would expect that an increased formation of glycine will be accompanied by an enhanced formation of N^5,N^{10}-methylene-FH_4 and its reaction products. Therefore, it is not inconceivable that, under these circumstances, methylene-FH_4 will accumulate and, as discussed above, may be split to form formaldehyde which will react with monoamines to yield isoquinolines or β-carbolines. The mechanism by which the increased glycine formation in porphyria is initiated is unknown.

Clinical characterization

To detect other patients suffering from the syndrome described, we scrutinized all patients who might belong to the group of schizoaffective psychotics. Table I shows the most common descriptive diagnoses which belong, accord-

Table I. Descriptive diagnoses belonging to the category of schizoaffective psychosis in which perceptual disturbances may occur

schizoaffective psychosis	reactive psychosis
atypical mania	remittent psychosis
degeneration psychosis	episodic psychosis
schizophreniform psychosis	oneirophrenia
motility psychosis	psychogenic psychosis
mixed psychosis	atypical psychosis
cycloid psychosis	

ing to some authors, to the broad category of schizoaffective psychosis. By far the most important consideration was, however, that the patients we were looking for would be suffering or have suffered from more or less circumscribed dysperceptions. These dysperceptions are not included in the description of schizoaffective psychosis in either the 'International Classification of Diseases' or 'Research Diagnostic Criteria' (Spitzer *et al.*, 1975). It was argued that the experience of dysperceptions could have been obscured or have become less important for patients overwhelmed by other symptoms such as anxiety, paranoid ideation, or hallucinations. It might also be possible that the influence of cognitive factors and interpretation based on personal factors would result in subjective statements by the patient in which the

perceptual anomaly is hardly detectable. For instance the conviction of one patient that he was an immortal saint was due to the perception of a small, white separate room as colorful and greatly enlarged, during a period in which a euphoric mood and a profoundly changed experience of passing time dominated.

To detect dysperceptions in patients, a questionnaire developed by El-Meligi and Osmond—the Experiential World Inventory (EWI)—was used. The EWI consists of 2 × 200 statements which the patient has to answer as true or false. The statements belong to one of eight categories. Categories 1–4 are more directly related to perception and experience, while categories 5–8 may be considered as related to mental processes of anomalous perception. The detection of changes in passing time was performed with the aid of an electronic metronome. The patient was asked to adjust the metronome to a frequency representing his personal assessment of passing time.

Biochemical characterization

All patients were screened for abnormal porphyrin biosynthesis and for homocystinuria. Some of the patients were found to suffer from porphyria, while none of the patients suffered from homocysteinuria. The seriousness of the psychosis was scored as presented in Table II. Scores 1–6 also represent

Table II. Behavioral scores related to the severity of psychosis

1. Anxiety
2. Dysphoria/euphoria
3. Depersonalization
4. Dysperceptions
5. Hallucinations
6. Catatonia

the sequence in the development of the psychosis. Because of the importance in methyl transfer and in porphyria of the serine–glycine conversion, via serine hydroxymethyltransferase, the excretion of these amino acids in the urine during different psychotic states was measured. Table III shows the excretion of serine, glycine, alanine, and tyrosine in 24-hour urine in relation to the psychotic state of the patients. Alanine represents another non-essential amino acid, while tyrosine can be regarded as a semi-essential amino acid, since it is derived from phenylalanine, an essential amino acid and also depends on the food intake. Table III contains the results of the first four patients suffering from dysperception or hallucinations. From this table it is clear that serine excretion decreased during psychosis. From these four

Table III. Excretion of serine, glycine, alanine, and tyrosine (as percentage of control) in relation to psychosis

	Behavioral score	Serine	Glycine	Alanine	Tyrosine
controls(3)	0	100 ± 23	100 ± 14	100 ± 39	100 ± 12
patients(4)	0	101 ± 26	85 ± 30	56 ± 20	82 ± 28
G.B. 3×†	2	74 ± 2	66 ± 3	73 ± 1	98 ± 10
G.B. 2×	4	49;54	46;36	53;43	70;78
E.M. 3×	5	2 ± 2	201 ± 48	78 ± 26	84 ± 24
D.S.* 1×	5	11	3	11	32
A.H.* 1×	6	39	35	18	15

Numbers in brackets indicate number of patients or controls.
* D.S. suffered from porphyria cutanea tarda; A.H. suffered from porphyria variegata
† the number of determinations on different days for the patient under the same psychotic conditions

patients, two were shown to suffer from porphyria (D.S. and A.H.). Glycine excretion also seemed to be decreased, although one patient (E.M.) showed an increased excretion of this amino acid during severe psychosis. The other two amino acids exhibited similar excretion patterns to those in controls, but the two patients suffering from porphyria showed a decreased excretion of amino acids. Nevertheless, from this experiment it seems that a common factor among these four patients may be an impaired excretion of serine during psychosis. Such a defect might point to an enhanced utilization of serine by the patients, which would be in agreement with the proposed hypothesis.

To obtain more direct information, it was decided to load the patients with low doses of serine or glycine (2 mmole kg^{-1}) and to observe their behavior. Patients and healthy controls were fed a carbohydrate-rich diet for at least four days before loading experiments were started. Blood samples were subsequently taken every hour over a period of 6 h after loading was initiated, for determination of serine and glycine.

As can be seen from Table IV, all patients loaded with serine or glycine necame psychotic to an extent varying from depersonalization to hallucinations. It is worth mentioning that the evoked psychotic symptoms, according to the patients, were identical to their 'natural' psychotic symptoms. Moreover, all patients seemed to respond favorably to the carbohydrate-rich diet and this response was not restricted to those who suffered from a proven porphyria. Some patients reacted with vegetative responses to glycine loading, which might be expected in porphyric patients. However, no explanation can be given at present for the fact that four out of five non-porphyric patients also reacted with vegetative symptoms in addition to the glycine-induced

Table IV. Schizoaffective disorders provoked by loading the patients with serine or glycine and their relation to porphyria, carbohydrate-rich diet and psychotic symptoms

Patient	Diagnosis	Porphyria	Response to diet	Behavioral score after loading with	
				Serine	Glycine
E.M.	Oneirophrenia	—	+++	3	4 (V)
G.B.	Schizophreniform psychosis	—	+	4	0
D.S.	Dysphoric-depersonalization syndrome	+	++	4	0 (V)
A.H.	Acute hallucinosis	+	+++	5	0 (V)
R.M.	Atypical psychosis	—	++	0	4 (V)
I.v.d.T.	Atypical mania	—	+	0	5 (V)*
H.V.	Atypical mania	—	++	0	5 (V)
A.v.D.	Psychogenic psychosis	—	?	4	4
P.W.	Degeneration psychosis	+	++	n.l.	n.l.
A.d.H.	Remittent schizophrenia	+	+++	n.l.	n.l.

n.l. = not loaded; (V) = vegetative symptoms; * = closed eyes imagery response to diet: +++ = total recovery, ++ = decrease in frequency of attacks and improvement with at least two scores, + = decrease in frequency of attacks
Behavioral score (see Table II)

psychosis. Although induction of psychotic symptoms, after loading the patients with glycine, does not, at first glance, seem to fit the hypothesis proposed, it is known that glycine can be converted into CO_2 and NH_3 by the glycine cleavage enzyme which simultaneously methylates FH_4 resulting in the formation of N^5,N^{10}-methylene-FH_4. This latter product can act as a substrate for cyclization of monoamines as discussed previously. Several interesting conclusions can be drawn from the data shown in Table IV. Firstly, it seems that the ability of ordinary non-essential amino acids, such as serine and glycine, to induce psychotic symptoms within about 5 h while having no effect in healthy controls, is without precedent in the literature. Secondly, the ability of a carbohydrate-rich diet (or glucose) to prevent psychotic attacks suggests that a peripheral rather than a central mechanism is involved in the pathogenesis of the described psychosis.

Analysis of the plasma samples drawn from the patients before and after loading with serine or glycine might be expected to reflect the activity of serine hydroxymethyltransferase. As can be seen in Fig. 3a, a linear relationship exists between the plasma levels of serine and glycine after loading with serine. However, in patient E.M., glycine formation reached a plateau at a plasma serine concentration of about 0.3 mM. Fig. 3b shows the relationship between the plasma levels of both amino acids after glycine loading. In controls, as well as most of the patients, a plateau in the increased formation of serine was seen after glycine loading, with the exception of

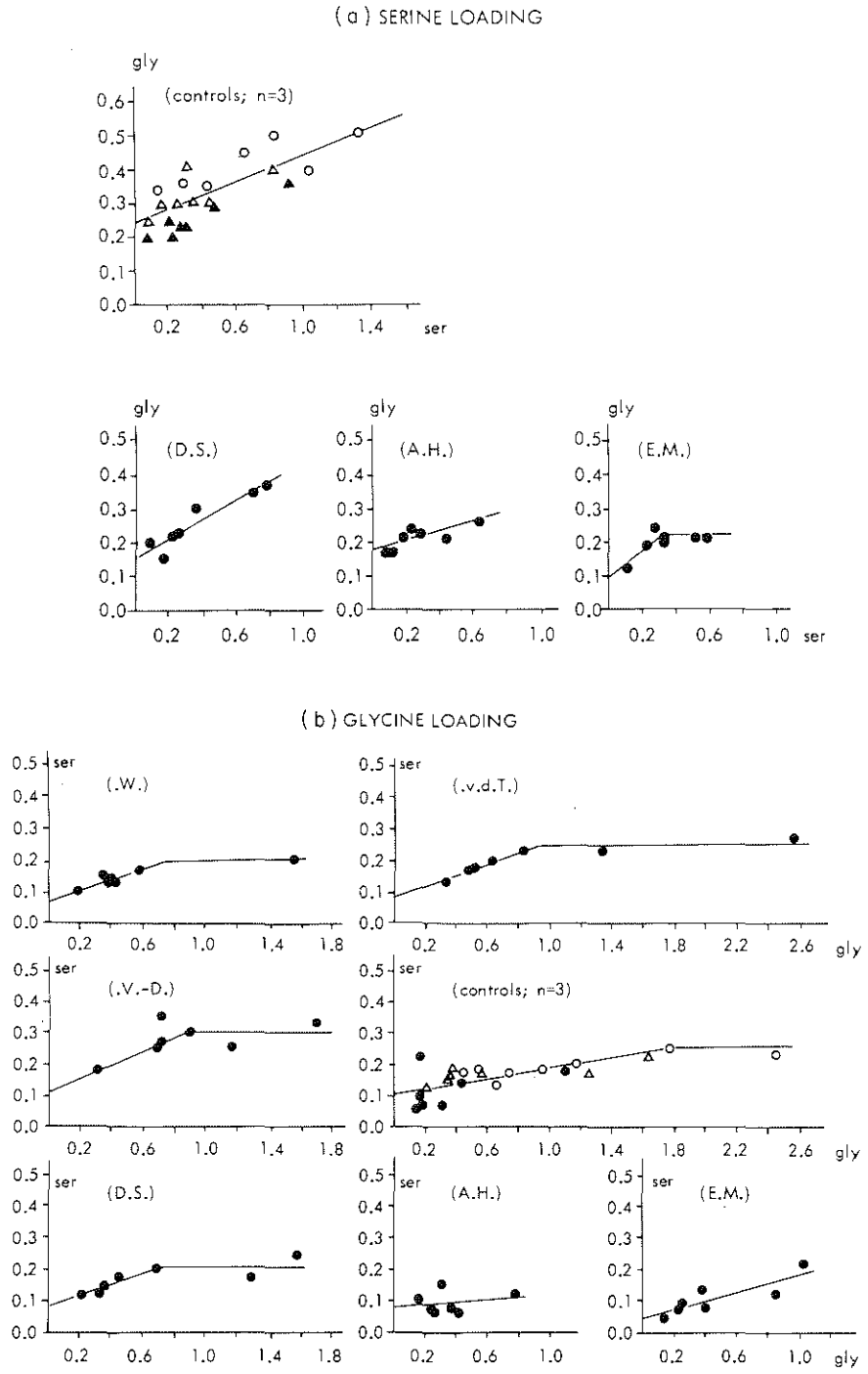

Fig. 3. Plasma levels of serine and glycine. (a) After serine loading; (b) After glycine loading

patients A.H. and E.M. In the first of these exceptional cases, no increase in plasma serine concentration was detectable and in the second case, the plasma concentration of serine did not achieve its plateau level (0.25 mM). A firm conclusion concerning the activity of serine hydroxymethyltransferase in relation to psychosis, however, is not permissible on the basis of these data, since serine and glycine are also involved in other biochemical reactions, as shown in Fig. 4. The slopes of the curves, indicating the increase in serine or

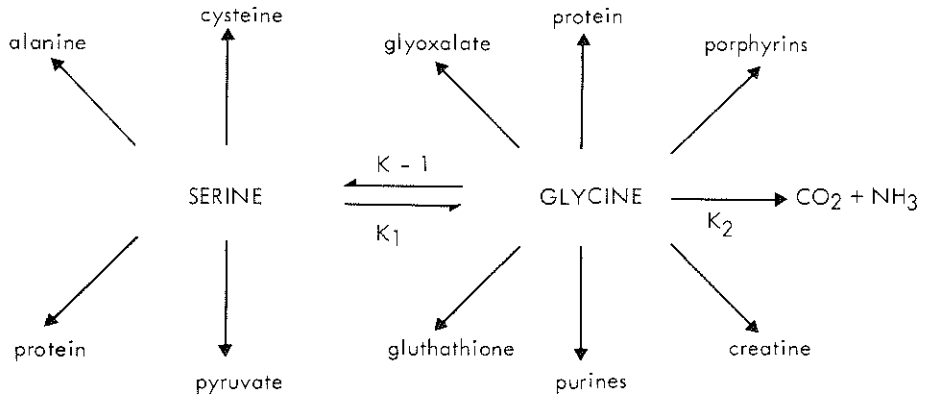

Fig. 4. Pathways in which serine and glycine act as precursors

glycine in plasma after loading the patients with glycine or serine, respectively, are presented in Table V. The limited data presented here do not permit firm conclusions to be drawn. Nevertheless, we have attempted to relate our findings to the proposed hypothesis and to account for any points of conflict, as outlined below.

Table V. Slopes of the curves shown in Figs. 3a and 3b as a measure of the increase in plasma glycine and serine after loading patients with serine or glycine (2 mmole kg^{-1}) respectively

	Loading	
	Glycine	Serine
Controls (3)	0.084 ± 0.012	0.200 ± 0.025
D.S.	0.179 ± 0.012	0.277 ± 0.028
A.H.	0.036 ± 0.033	0.136 ± 0.023
E.M.	0.141 ± 0.020	0.683 ± 0.031
P.W.	0.172 ± 0.008	n.d.
I.v.d.T.	0.176 ± 0.002	n.d.
A.v.D.	0.218 ± 0.019	n.d.

n.d.: plasma glycine after serine loading has not yet been determined

Possible interpretation of biochemical data

The increase in the production of serine, after glycine loading, in four out of six patients (Fig. 3a and Table V) might be explained in two ways:

(1) An impaired metabolism of serine.
(2) An increased conversion of glycine into serine as the result of activated serine hydroxymethyltransferase.

Since the reaction catalyzed by serine hydroxymethyltransferase is an equilibrium reaction, both mechanisms could account for the increased level of glycine. However, explanation (1) seems less probable because the excretion of serine, as shown in a limited number of patients, was decreased and not increased during psychosis (Table I). In addition, normal or low plasma levels of serine were found in these patients (Fig. 3a). The second explanation would appear to fit the results better. Any activation of serine hydroxymethyltransferase would, as discussed above, result in an activation of both conversions: serine into glycine and glycine into serine. However, the serine–glycine conversion, as shown in Fig. 3b, seems to have been increased by only 40% in patient D.S. while the glycine–serine conversion was increased by 100%. This difference may have been caused by porphyria, since the available glycine might then be used for the biosynthesis of porphyrins. This also holds for patient A.H. who, in fact, exhibited no increase in plasma serine at all after glycine loading, while the serine–glycine conversion seems to have been within the normal range for this patient. However, in this patient, the serine–glycine conversion might also have been enhanced, because the glycine formed could, as discussed above, have contributed, in part, to an increased porphyrin biosynthesis. The finding that, in these two patients, only serine loading resulted in psychotic symptoms supports the proposed hypothesis that serine–glycine conversion and the concomitant formation of N^5,N^{10}-methylene-FH_4 is responsible for the induction of psychosis.

Glycine–serine conversion in patient E.M. also seems to have increased by 70%, suggesting an increased activity of serine hydroxymethyltransferase and the induction of psychotic symptoms after serine loading supports this suggestion. However, in the loading experiment with glycine, this patient reacted differently from the other patients in that, under these conditions, psychotic symptoms also arose. Although this psychosis was accompanied by vegetative symptoms, which would favor a diagnosis of porphyria, no evidence for an abnormal porphyrin biosynthesis cold be detected. Moreover, the two porphyric patients did not show psychotic symptoms after loading with glycine, as was the case with patient E.M. and another four patients (see Table IV). From the different reactions initiated following the use of glycine as a substrate, that forming $CO_2 + NH_3$ seems to fit the proposed hypothesis

the best. As discussed above, the enzyme involved in this reaction is the glycine cleavage enzyme by which a one-carbon transfer takes place from glycine to FH_4, resulting in the formation of methylene-FH_4. Therefore, it is suggested that both enzymes, serine hydroxymethyltransferase and the cleavage enzyme, were activated in this patient. The finding that, in this patient, glycine excretion was increased during psychosis (see Table I) seems to be in agreement with this suggestion.

Patient A.v.D. also showed psychotic symptoms after glycine loading and exhibited an increase in the glycine–serine conversion of about 260%. Although no data are available at the moment on glycine formation, the same dysfunction as described for patient E.M. might be applicable, since patient A.v.D. also reacted with psychotic symptoms after loading with serine as well as after loading with glycine.

In the other two patients who showed a positive reaction to glycine loading (I.v.d.T and H.V., see Table IV) and who did not show any symptoms after serine loading, an increased activity of the cleavage enzyme might be held responsible for the induction of psychotic symptoms. It is noteworthy that loading two of the patients with methionine (2 mmole kg^{-1}) did not provoke psychotic symptoms in contrast to other reports (Pollin *et al.*, 1961; Antun *et al.*, 1971). However, in the earlier experiments, patients had to be treated with methionine for at least two days before psychotic symptoms arose, while in the present experiments, psychotic symptoms arose about 5 h after loading with serine and glycine.

In summary, the results obtained from patients after loading with serine and glycine seem to support the proposed hypothesis that an increased formation of N^5,N^{10}-methylene-FH_4 is responsible for the induction of psychotic symptoms. The increased formation of methylene-FH_4 might be due to an enhanced activity of serine hydroxymethyltransferase which may or may not be coupled to porphyria. Patients who suffer from this dysfunction may become psychotic after serine loading. The psychotic symptoms induced after glycine loading, as shown in a second group of patients, might be caused by an increased activity of the glycine cleavage enzyme, which also yields methylene-FH_4. A combination of both dysfunctions seems also possible, with a common factor responsible for triggering these reactions. A possible candidate might be the enhanced demand for glycine when the biosynthesis of ALA is increased. This might not only be the case in patients who suffer from porphyria but also in non-porphyric patients during stress or during a premenstrual period when plasma levels of corticosteroids and estrogens, respectively, are increased. These hormones increase porphyrin biosynthesis by increasing the activity of ALA-synthetase, the rate-limiting enzyme of porphyrin biosynthesis. Induction of cytochrome P-450, a porphyrin-containing enzyme involved in drug metabolism, by drugs such as barbiturates or sulfonamides, might also induce psychotic symptoms by increasing

porphyrin biosynthesis (see also De Matteis and Rimington, 1962). On the basis of these possibilities an explanation may be offered for the beneficial effects of a carbohydrate-rich diet or of glucose not only in porphyric but also in nonporphyric psychotic patients, namely, by decreasing ALA-synthetase activity.

CONCLUSION

A group of patients who were suffering from schizoaffective psychosis and who showed distinct perceptual disturbances other than hallucinations was selected. In contrast to other studies on schizophrenia, the symptoms of these patients were shown to be related to transmethylation. In general, the therapeutic effect of the prescribed carbohydrate-rich diet was found to be superior to treatment with neuroleptics.

The induction of psychosis by loading patients with serine or glycine seems to be in accordance with the proposed hypothesis that an increased formation of N^5,N^{10}-methylene-FH_4 might be a common factor in this group of patients related to perceptual disturbances. We are well aware, however, of the fact that the evidence presented is indirect. Studies are planned in which we hope to obtain more direct evidence for the proposed hypothesis. In addition, experiments are in progress which should indicate the specificity of the loading test in patients suffering from the described type of schizoaffective psychosis.

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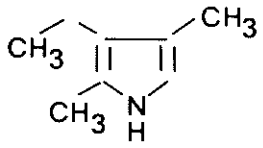
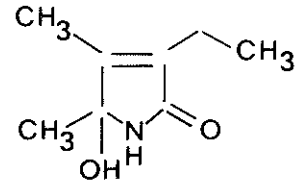
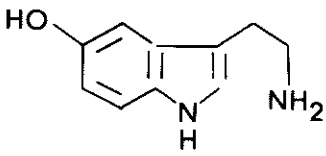
STRUCTURAL FORMULAE



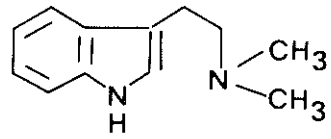
kryptopyrrole = 2,4 dimethyl-3-ethylpyrrole



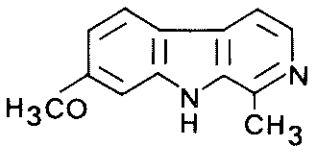
haemopyrrole lactam = hydroxy haemopyrrolin-2-one, OH-HPL



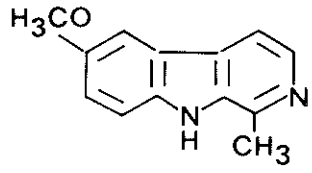
5-hydroxytryptamine (serotonine)



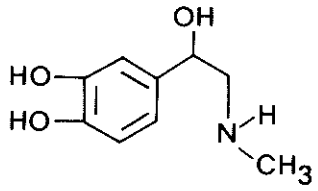
dimethyltryptamine (DMT)



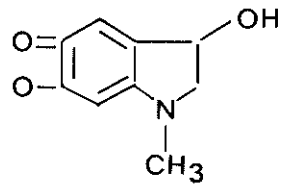
harmine



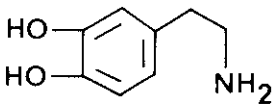
6-methoxyharmalan



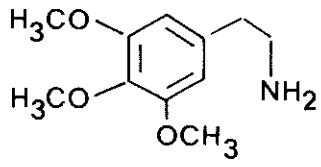
adrenaline



adrenochrome



dopamine



mescaline

NASCHRIFT

Op deze plaats wil ik al diegenen danken die mij bij het onderzoek en de bewerking van het proefschrift hebben geholpen en bijgestaan.

Mijn beide promotoren ben ik veel verschuldigd.
Zonder de neurechemische kennis van prof. Bruinvels en zijn vindingrijkheid op dit gebied zou de centrale hypothese van dit proefschrift nooit zijn geboren.
Evenmin zou dit proefschrift tot stand zijn gekomen zonder de "klassieke" - in de beste zin van het woord - diagnostische kennis van prof. Ladee. Met vrucht heb ik vooral van dit aspect geprofiteerd bij de herkenning van de in dit proefschrift beschreven patiënten.

De leden van het eerste uur van de Werkgroep Biologische Psychiatrie, Willem Blom, Ruud van Tuijl en Peter Moleman, ben ik zeer erkentelijk voor hun aandeel in het onderzoek en hun adviezen tijdens de bewerking van de verschillende hoofdstukken.

De verpleegstaf van onze afdeling, met name Geert Jurgens en Pierre Reijnders, komt alle lof toe voor hun medewerking bij de observaties en het extra werk dat het onderzoek met zich mee bracht.

De beide co-referenten, prof. Sanders-Woudstra en prof. Wilson, dank ik voor hun opmerkingen die tot zinvolle verbeteringen van het manuscript hebben geleid.

Voor het uitgebalanceerde diëtaire werk wil ik hier Ineke Kersten danken; Tiny Zaanen en Tineke Jansse verdienen veel lof voor het vele, vele en uiteindelijk doorslaggevende typewerk; Hans Baay en Klen Sibbel deden de middelbare scholier in mij herleven door hun correcties van de Engelse teksten.
Ir. P.I.M. Schmitz bespaarde mij veel onnodig werk als gevolg van zijn adviezen bij de opzet en uitwerking van het onderzoek.

CURRICULUM VITAE

De schrijver van dit proefschrift is geboren op 20 december 1943 te Leeuwarden, alwaar hij van 1957 tot 1962 de HBS-B doorliep.

Met de studie Geneeskunde werd na het behalen van het eindexamen in 1962 aan de Rijksuniversiteit te Groningen begonnen. Tijdens deze studie was hij enkele jaren student-assistent op het Histologisch Laboratorium onder leiding van prof.dr. F.J. Keuning, en na het semi-artsexamen tijdelijk assistent op de afdeling voor Chronische Aspecifieke Respiratoire Aandoeningen van het Sanatorium Beatrixoord te Haren (Gr.).

Na het behalen van het artsexamen in juli 1970 was hij tot april 1971 werkzaam als waarnemend huisarts in diverse praktijken.

Opleiding tot psychiater geschiedde op de afdeling Psychiatrie van het Academisch Ziekenhuis Rotterdam-Dijkzigt onder leiding van prof.dr. G.A. Ladee. Het stagejaar Neurologie werd eveneens in voornoemd ziekenhuis doorlopen onder leiding van prof.dr. A. Staal.

Per 1 mei 1975 is hij ingeschreven in het Nederlands Specialisten Register en sindsdien werkzaam als hoofd-wetenschappelijk medewerker in dienst van de Erasmus Universiteit Rotterdam op bovengenoemde afdeling Psychiatrie (hoofd: prof.dr. G.A. Ladee).

Sinds 1977 is hij secretaris van het Interdisciplinair Genootschap voor Biologische Psychiatrie.