Clinical Neuropharmacology

Volume 1

Edited by

Harold L. Klawans, M.D.

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Raven Press ▪ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

International Standard Book Number 0–89004–035–4
Library of Congress Catalog Card Number 75–14581

Preface

For many years I have felt that there is a lack of good source material in clinical neuropharmacology and in the correlation between basic neuropharmacology and clinical therapeutics. Despite the marked proliferation of printed material in almost all fields of medicine, this void has not been adequately filled. In recent years I have contemplated several solutions to this problem, including a single author textbook, a multiple author textbook, or a journal devoted to clinical neuropharmacology, but for a variety of reasons all of these solutions were discarded.

The concept of an ongoing series of volumes containing authoritative reviews of the various problems of neuropharmacology evolved from a conversation with Dr. Alan M. Edelson of Raven Press at the Tenth International Congress of Neurology held in Barcelona in September 1973. Over the next year, we pursued this concept and finally decided to launch this series under the title *Clinical Neuropharmacology*. The series will attempt to cover the clinical pharmacology of the nervous system in the broadest sense. All too often clinical pharmacology is viewed as a limited field concerned almost exclusively with blood levels, drug interactions, and side effects, while concepts of mechanism of action are considered part of basic pharmacology, and the use of drugs to treat specific systems is disdained as therapeutics. It is my view that clinical pharmacology is the overall study of the effects of drugs in man and that a thorough understanding of clinical neuropharmacology must include clinical neurophysiology, basic pharmacology, and therapeutics as well as those subjects usually grouped as clinical pharmacology.

In order to deal with this entire field, a broad range of topics must be explored, ranging from the therapeutics of specific signs or symptoms such as raised intracranial pressure (Chapter 7) and spasticity (Chapter 6) to critiques of the physiologic or biochemical basis of neurologic disorders commonly treated pharmacologically (Chapter 8). Since neuropharmacology is the study of the effects of drugs on the nervous system, the subject matter will also range from purely neurologic problems such as spasticity to such traditionally psychiatric problems as schizophrenia (Chapter 1). Classic problems of clinical pharmacology, such as drug metabolism and drug interaction, will be included as will relevant preclinical studies of the basic mechanism of drug actions. Authors with clinical and, when possible, basic pharmacologic expertise will be invited to write up-to-date reviews of each subject. (Since the major concern of this series is pharmacology and not therapeutics, experimental agents may often be included in the various contributions. Any decision to exclude such agents would be both pro-

vincial and self-defeating. A drug that may be experimental in the United States may be in general use elsewhere. An example of this is baclofen which is discussed by Dr. Calne in Chapter 6. It is hoped that the decision to include pertinent discussion of such agents will not be discomforting to most readers.)

In any book depending on multiple authors, some authors are invariably more prompt in completing their manuscripts. The tardy paper or two can delay publications for unconscionably long periods of time, resulting in numerous problems for the editor and the other authors whose manuscripts are aging. In order to avoid this problem, it was decided that a new volume would appear as soon as a sufficient number of articles were received and reviewed. Although this might cause some problems in the logic of the design of each volume, this format will keep the delay between writing and publishing to a minimum.

This first volume is made up of nine contributions. Despite the policy of publishing articles in the order of their being received rather than preplanning an entire volume, several of the chapters are closely related. Chapter 1 (by Harold L. Klawans, Christopher Goetz, and Ruth Westheimer) is primarily an essay on the pharmacology and pathophysiology of schizophrenia. Its inclusion may reflect either an increasing awareness of the biologic basis of this syndrome or the editor's own prejudice that this disease reflects disordered neurologic functions. Chapter 2 (by Daniel Tarsy and Ross J. Baldessarini) focuses on an unfortunately frequent and often irreversible complication of the neuroleptic treatment of schizophrenia, whereas Chapter 3 (by Robert P. Granacher and Ross J. Baldessarini) deals in part with anticholinergic toxicity often seen in "psychiatric" patients receiving neuroleptics and concurrent anticholinergic therapy. Chapter 4 (by Richard D. Sweet, Ruth D. Bruun, Arthur K. Shapiro, and Elaine Shapiro) explores a syndrome—Gilles de la Tourette—that has long occupied the borderline between neurology and psychiatry, but that is now becoming recognized as a neurologic disorder because of the careful pharmacologic work of these authors and others.

Malnutrition, especially avitaminosis, has long been recognized as a cause of neurologic dysfunction. Since their discovery, virtually all vitamins have been used in the care of patients with various neurologic disorders although their therapeutic role has only occasionally been well documented. Chapter 5 (by William J. Weiner) explores the role of a specific vitamin—vitamin B_6—in both the etiology and treatment of neurologic disorders.

Chapters 6 through 8 (by Donald B. Calne, Leon D. Prockop, and Howard L. Fields and Neil H. Raskin) discuss the therapeutic and basic pharmacology of specific neurologic states, whereas the last chapter (by George W. Bruyn) is a thorough review of the biochemical basis of a syndrome—migraine—in which the empiric therapeutics are better understood than the biochemistry.

Future volumes will cover such topics as:

1. The pharmacology of tremor
2. The diagnosis and management of sleep disorders
3. The pharmacology and therapeutics of cerebral ischemia
4. Management and pharmacology of multiple sclerosis
5. Prevention and management of the side effects of levodopa
6. Kinetics of levodopa absorption and metabolism
7. The pharmacology of depression
8. The pharmacology of myotonia
9. The pharmacology of status epilepticus
10. The pharmacology of myasthenia gravis

Whether or not this series serves the purpose for which it was designed, or any other purpose, can be determined only by the readers. If these books are at all successful, the credit goes to the various authors; if they are not, this should reflect only on the judgment of the editor.

Harold L. Klawans
(*August 1975*)

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Contents

Clinical Neuropharmacology, Vol. 1, edited by
H. L. Klawans. Raven Press, New York © 1976.

Chapter 1

The Pharmacology of Schizophrenia

Harold L. Klawans, Christopher Goetz,
and Ruth Westheimer

Neither the etiology nor the pathogenesis of schizophrenia is known. Biochemical toxicity, environmental stress, and hereditary or enzymatic abnormalities have all been suggested as possible origins of the disease. Attempts to integrate these diverse theories are often incomplete and vague. We have previously proposed a model for integrating these many theories and for reviewing the past and current research in schizophrenia (1). This model is derived from pharmacology and theories of drug-cell interactions. This model is not an explanation of the etiology of schizophrenia but is a description of the pathophysiology of the clinical state. It is based on the premise that a small molecule (drug, neurotransmitter) acts on a large molecule (receptor site) in order to produce a specific effect. This can be expressed as:

$$SM_x + RS_x \rightarrow Effect_x,$$

where SM stands for a specific small molecule (e.g., dopamine) and RS for a specific receptor site (e.g., dopaminergic receptor site). The subscripts indicate the characteristics of the small molecule, receptor site, or effect (e.g., normal, abnormal, schizophrenic). The arrow indicates that the interaction of the small molecule and the receptor site will lead to a specific, excitatory or inhibitory, effect on the postsynaptic membrane. The sum of all the individual excitatory and inhibitory influences on a given neuron at any time will determine whether or not that neuron fires. The complex pattern of similar influences on a large number of neurons will determine the behavior of the organism. Overall behavior is the result of numerous specific effects. Thus,

$$\text{Behavior} = \sum_{x=1}^{n} \text{Effect}_x, \text{ where } SM_x + RS_x \rightarrow \text{Effect}_x.$$

Alterations in this process can participate in the production of abnormal behavior. Throughout this discussion, the effect of a particular small molecule-receptor site interaction will be subscripted "schizophrenia" to

indicate that the specified interaction is thought to participate in the elaboration of schizophrenic behavior.

From the perspective of this model, behavior can be affected through an alteration in any one of three variables. An abnormal small molecule, acting at a normal receptor site may act to alter the firing of a single neuron, and thereby alter the balance of a multineuronal circuit. The ultimate result of this alteration could be schizophrenic behavior.

$$SM_{abnormal} + RS_{normal} \rightarrow Effect_{schizophrenia}.$$

Investigators who have attempted to explain schizophrenia in terms of a defect at the level of the small molecule include Osmond and Smythies (2) (dimethoxyphenethylamine, DMPEA), Johnson et al. (3) (*N*-acetyldimethoxyphenethylamine, NADMPEA), Hoffer et al. (4) (adrenochrome), and Antun et al. (5) (methionine). Although each group pursued the isolation of a different individual chemical, they all aimed to demonstrate that the abnormality in schizophrenia involves the production of an abnormal small molecule ($SM_{schizophrenia}$). This molecule then acts on the normal brain (RS_{normal}) to produce altered behavior ($Effect_{schizophrenia}$).

The implication of such theories is that schizophrenia is a normal response of a normal brain to stimulation by an abnormal small molecule. Any investigator who gives small molecules (which may be abnormal in quality or quantity) to normal individuals in an attempt to generate schizophrenia must assume that schizophrenia is part of the brain's normal repertoire of potential responses. They must assume that, under the appropriate stimulation, everyone has the potential to become schizophrenic.

The second parameter in the model is the large molecule or RS. A normal SM acting at this altered RS will induce an abnormal effect at that specific neuron and further alter the balance of larger neuronal networks.

$$SM_{normal} + RS_{schizophrenia} \rightarrow Effect_{schizophrenia}.$$

Investigators who have studied the large molecule or RS abnormalities in relation to schizophrenia include Heath et al. (6) (taraxein, a gamma-G-immunoglobulin) and Frohman (7) (proteins isolated from schizophrenics that alter cellular metabolism and neuronal function). Although the protein defects demonstrated by each group are different, they both suggest that the causative defect in schizophrenia is at the cellular membrane. Normal amounts of normal transmitter are misinterpreted at the receptor site and thereby lead to abnormal behavior. The assumption made by these investigators is that the brains of schizophrenics are inherently abnormal, such that abnormal behavior is effected even with normal small molecule stimulation.

Finally, the third parameter of the model must be considered. A normal small molecule may act at a normal receptor site in the brain and still result in an abnormal effect.

$$SM_{normal} + RS_{normal} \rightarrow Effect_{schizophrenia}.$$

Multisynaptic pathways and inputs beyond the initial receptor site will, of necessity, modify the quality of the effect generated by any single small molecule as it acts at its receptor site. Past experience, environmental stress, and emotional reinforcement can in this way alter the manner in which neuronal information is handled and manifested. The theories of an environmental etiology for schizophrenia—including Sullivan's "disturbed mother-child relationships" (8), Arieti's "rearoused childhood anxieties" (9), Wynne et al.'s "distorted interpersonal relationships and communications" (10)—are applicable to this parameter of the model.

With the use of this model, a number of observations can be made that make it easier to understand the pharmacology of schizophrenia. The first is that the drug therapy used in the treatment of schizophrenia is compatible with a defect in any of the three parameters of the model. Although there is much disagreement as to the pathogenic defect in schizophrenia, either small molecule, receptor site, or environment, there is agreement that the appropriate drug therapy involves the neuroleptic agents (11,12). The one characteristic shared by all neuroleptic agents is that they block selective receptor sites in the brain (13,14). Thus, if the pathogenic defect is a small molecule that acts at those selective receptor sites, the blockade of such receptors would prevent neuronal firing and the generation of an abnormal effect. Alternatively, if the defect is at the receptor site, the neuroleptics will be effective therapy because the receptor site will be blocked and abnormal neuronal firing will be interrupted. Finally, if the environment is the pathogenic basis of schizophrenia, the blockade of selective receptor sites will alter the input of the multineuronal circuits and thereby alter behavior. In this way, a drug that has a single mechanism of action can nevertheless alter behavior that is generated through different types of defects.

This model is further useful in integrating the concepts of the pathogenesis and pathophysiology of schizophrenia. The pathogenesis of schizophrenia refers to the primary defect, either small molecule, receptor site, or environment, whereas the pathophysiology refers to the manner in which this primary defect will alter normal neuronal function. Only when it is considered in the perspective of neuronal physiology does the significance of the primary pathogenic defect in the production of alterations in behavior become evident. The model as a whole represents the pathophysiology of schizophrenia; the individual variables represent the possible pathogenic defects.

It is our belief that the pathophysiology of schizophrenia is related to the dopaminergic system of the brain. Areas of highest dopamine levels are the nigrostriatal system of the basal ganglia, the subcortical mesolimbic system, the hypothalamus, and, in the rat, scattered areas of the limbic cortex. The

limbic cortical areas of dopamine have been determined by histochemical techniques and include the gyrus cinguli, the entorhinal cortex, the lateral posterior amygdaloid cortex, and the most basal layers of the dorsal frontal cortex (15). Although the several symptoms of schizophrenia may seem more probably related to cortical dysfunction than basal ganglia disease, dopamine-mediated interconnections between the deep brain centers and the limbic cortex are numerous. Because of these interconnections, a dysfunction of dopaminergic neurons in the deeper centers could conceivably effect the changes in personality, mood, and thought processes that are characteristic of schizophrenia.

The physiology of the normal dopamine system in terms of the proposed model can be expressed as:

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{normal}} \rightarrow \text{Effect}_{\text{normal}},$$

where DA-RS is the dopamine receptor site. An abnormal effect can be generated by abnormalities in the concentration or structure of the small molecule, in the structure or availability of the receptor site, or in multineuronal circuits that infiuence dopaminergic physiology. We propose to evaluate the accumulated evidence at the level of the small molecule and receptor site in relationship to the possible role of dopamine in the pathophysiology of schizophrenia. There is evidence that the dopaminergic system may be involved in the pathophysiology of schizophrenia at any of the three parameters of the model. We feel that the experimental data are most consistent with the hypothesis that an abnormality at the level of the dopamine receptor site is of pathophysiologic significance in schizophrenia.

AMPHETAMINE PSYCHOSIS

One approach to the study of a disease with unknown etiology is to attempt its replication either in animals or humans. The psychosis associated with chronic amphetamine addiction can mimic acute schizophrenia, and has been proposed by many authors as a working model of the disease (16,17). Amphetamine psychosis is characterized by paranoid delusions, auditory and visual hallucinations, and stereotyped behavior (18). Although it is reported that patients suffering from amphetamine psychosis lack the thought disorder characteristic of schizophrenia, the similarity between the two states is such that in many cases they are indistinguishable even to trained observers (19).

The action of amphetamine is known to involve the dopaminergic system. Amphetamine causes the release of dopamine from nerve terminals in the striatum, and elsewhere, thus making more dopamine available to act on the dopamine receptors (20,21). The stereotypy seen in experimental animals treated with amphetamine is the accepted behavioral model for increased

activity in the dopaminergic system (22). Amphetamine-induced stereotyped behavior is used for testing the efficacy of new drugs aimed at altering dopaminergic physiology (23–26).

Because amphetamine acts to increase the amount of dopamine acting at the dopamine receptor site, its role in initiating the schizophrenia-like psychosis may be viewed in the terms of the model as:

$$\text{Dopamine}_{\text{abnormal amount}} + \text{DA-RS}_{\text{normal}} \rightarrow \text{Effect}_{\text{schizophrenia}}.$$

The overstimulation of normal receptor sites in the striatum with increased amounts of newly released dopamine could initiate an abnormal behavioral pattern.

This role of amphetamine acting to alter the concentration of dopamine in the brain is consistent with the accepted concept of amphetamine as an indirect dopamine agonist. Rather than acting directly at the dopamine receptor site, amphetamine stimulates the receptor site indirectly by causing the release of presynaptic dopamine. The significance of a psychosis associated with increased dopamine stimulation is that schizophrenia, or a similar clinical picture, may be induced by too much dopamine acting on a normal brain substrate ($\text{RS}_{\text{normal}}$).

The data on amphetamine psychosis, however, may be interpreted in another manner. Recent experiments in our laboratory (27) suggest that in addition to its role of increasing presynaptic dopamine release, amphetamine may alter dopamine physiology at the level of the dopamine receptor site. Amphetamine in chronic doses may be acting to alter the striatal dopamine receptor sites to render them differentially responsive to dopamine.

In our laboratory we have defined the threshold dose for acute amphetamine-induced stereotypy in guinea pigs. Amphetamine is known to produce stereotyped behavior in a wide variety of animals. In guinea pigs, the behavior consists of simple, repetitive persistent movements involving the head, facial musculature, and mouth parts. The stereotyped behavior can be produced either by a single injection of amphetamine or by chronic exposure to the drug. To define better the action of amphetamine, we compared the doses of amphetamine necessary to elicit stereotypy in the acute versus chronic situations.

Animals were treated with a subthreshold dose of amphetamine each day for 3 weeks. One week after this pretreatment, the animals were again challenged with the subthreshold dose of amphetamine. All animals demonstrated amphetamine-induced stereotyped behavior at this subthreshold dose. Chronic exposure to low-dose amphetamine had clearly altered the amphetamine threshold for stereotypy.

To clarify the mechanism and cellular location of amphetamine action, we studied the effect of apomorphine on these amphetamine-pretreated animals. Apomorphine is a direct dopamine agonist and acts directly at the dopamine receptor sites (28,29). Apomorphine can generate the same animal

stereotypy as amphetamine, but, unlike amphetamine, it is a direct receptor site stimulant and does not involve the release of presynaptic dopamine. We demonstrated that chronic low-dose amphetamine exposure also reduces the threshold for apomorphine stereotypy. Since the apomorphine effect is known to be only postsynaptic, amphetamine must be acting to alter not only the mechanisms of presynaptic dopamine release but also to alter the postsynaptic membrane response. Evidence from other laboratories supports this concept of postsynaptic amphetamine activity. Lewander demonstrated in rats (30) and guinea pigs (31) that after chronic amphetamine administration, brain catecholamine levels were significantly decreased. Additionally, in rats after chronic amphetamine exposure, the pattern of urinary amphetamine metabolites remains constant (30). No new amphetamine by-product or metabolite could account for the measured decrease in catecholamine levels. These observations suggest that functional or structural alterations in the dopamine receptor site rather than changes in amphetamine or catecholamine metabolism are responsible for the dopaminergic supersensitivity that occurs following chronic amphetamine administration. This drug-induced alteration may consist of a direct modification of the dopamine receptor or a suppression of another neural mechanism that normally antagonizes amphetamine stereotypy. In terms of the drug-cell interaction model, the animals pretreated with chronic low-dose amphetamine can be described as:

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{abnormal}}.$$

If amphetamine alters human receptor sites in a similar way, the physiology of the schizophrenia-like psychosis seen in chronic amphetamine abuse could be explained in terms of distorted receptor sites. It is probable that a similar distortion of dopamine receptor sites of schizophrenic patients could account for the psychotic behavior seen in that disease.

It would be of clinical significance to define better the cellular mechanisms involved in amphetamine psychosis. Although amphetamine can generate both increased concentrations of small molecules and altered receptor sites, it is clear from the above experiments that hypersensitivity to amphetamine and apomorphine in animals is induced only after chronic amphetamine exposure. Similarly, the psychosis associated with amphetamine abuse in humans is usually seen only after long-term amphetamine addiction (19). With continued drug administration, the paranoia begins sooner, reaches a greater intensity, and may last longer after the drug is withdrawn. This increased sensitivity is maintained even after a prolonged abstinence from the drug (32). These characteristics of amphetamine psychosis are similar to the decreased latency, decreased threshold, and increased intensity of amphetamine-induced stereotyped behavior demonstrated in guinea pigs after chronic amphetamine administration. This raises the possibility that receptor site alterations are the cellular foundation of psychotic behavior

in amphetamine addicts. If this is so, the same or similar receptor site alteration may be the basis of schizophrenic behavior:

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{schizophrenia}}.$$

HUNTINGTON'S DISEASE

The amphetamine psychoses have been used as a possible human model in the study of schizophrenia. Using a disease whose etiology is well understood, investigators have aimed to clarify a disease whose etiology is not clearly understood. Other investigators have approached the problem of schizophrenia differently. They have searched for various medical diseases whose presentation may include a schizophrenia-like behavior, and have attempted to link the primary organic pathology of the medical disease to the physiology of the schizophrenic.

Schizophrenia accompanies or presents as the initial manifestation of several different neurologic diseases. In particular, Huntington's disease, a hereditary disorder characterized by progressive mental deterioration and choreatic movement disorders, has been linked to schizophrenia by numerous authors. Rosenbaum (33), Werner and Folk (34), and Bolt (35) reported frequent hallucinations and paranoid assaultive behavior in patients with Huntington's disease. Brothers (36) regards schizophrenia as the most common disease accompanying Huntington's chorea. Paulson (*personal communication*) has mentioned that, in his experience, approximately one-third of all Huntington's chorea patients in chronic hospitals were admitted with a diagnosis of schizophrenia. Van Putten and Menkes (37) in the space of 4 months encountered two definite cases of Huntington's chorea on a 30-bed psychiatric ward of chronic schizophrenics. These patients first masqueraded as schizophrenics, and then as schizophrenics with a phenothiazine-induced movement disorder.

The association of diagnosed schizophrenia in the history of patients with Huntington's chorea suggests that the pathophysiology of schizophrenia seen in Huntington's chorea may be related to the pathophysiology of the choreatic signs and symptoms. This pathophysiology is thought to involve abnormal dopamine receptor sites (36,37). The role of dopamine in the pathophysiology of chorea is clearly shown by analyzing the pharmacology of chorea. Drugs that block dopamine receptors (neuroleptics) and drugs that decrease brain levels of dopamine (reserpine, alpha-methyl-*para*-tyrosine) improve chorea, whereas drugs that increase brain dopamine content (levodopa) worsen chorea (36). Since brain dopamine levels are normal or decreased in Huntington's chorea and since the levels of homovanillic acid, the acid metabolite of dopamine, are known to be normal in Huntington's chorea (38), the exaggerated movements seen in this disease are presumably not due to increased concentrations of dopamine. It is suggested that choreatic movements are due to an exaggerated or altered

facilitatory effect of normal amounts of dopamine acting on altered neurons (38). The interaction of normal small molecules with abnormal receptor sites causes the neurons to fire abnormally.

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{abnormal}}.$$

Receptor site theory suggests that the causative defect in Huntington's chorea is at the cellular membrane, so that normal amounts of normal neurotransmitter are misinterpreted and thereby lead to abnormal behavior. The high incidence of schizophrenia in association with a disease involving abnormal neuronal receptor sites would suggest the possibility that a similar pathological mechanism underlies the two diseases.

The pathophysiology of psychosis seen in Huntington's chorea may be related to the pathophysiology of the choreatic signs and symptoms of Huntington's chorea and to the pathophysiology of psychosis seen in other disease states. It is possible that the similar mechanisms of these states may involve dopamine receptor sites that are altered in such a way as to be hypersensitive to dopamine. In terms of the model:

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{chorea}}$$

and

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{schizophrenia}}.$$

The structure and concentration of dopamine in patients with Huntington's chorea are normal, but the manner in which the chemical information is handled clearly is not.

The theory of receptor site hypersensitivity in Huntington's chorea has a number of clinical implications. Since Huntington's chorea patients are especially sensitive to dopamine stimulation, their choreatic movements are severely aggravated by the administration of levodopa in doses that normal subjects tolerate with no effect. Increasing the concentration of the normal small molecule will further aggravate the receptor site abnormality and intensify the abnormal end effect, such that

in choreatic patients

$$\text{Dopamine}_{\text{normal}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{chorea}},$$

and in choreatic patients with levodopa

$$\text{Dopamine}_{\text{increased amount}} + \text{DA-RS}_{\text{abnormal}} \rightarrow \text{Effect}_{\text{increased chorea}}.$$

Huntington's chorea is inherited according to an autosomal dominant pattern but usually does not become manifest until middle age (39). The defective genotype remains undetected, and most patients are asymptomatic until after the age of 30, when their children are already conceived. If the primary defect of Huntington's chorea involves an abnormally sensitive response of striatal neurons to dopamine, it may be possible to detect Huntington's chorea in presymptomatic subjects at risk for this disease.