Psychosis Associated with Hereditary Disorders

I. Herbert Scheinberg

American Handbook of Psychiatry

Psychosis Associated With Hereditary Disorders

I. Herbert Scheinberg

e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 4* edited by Silvano Arietti

Table of Contents

Introduction

Huntington's Chorea

Wilson's Disease

Acute Intermittent Porphyria

Discussion

Genetic Terminology

Bibliography

Notes

PSYCHOSIS ASSOCIATED WITH HEREDITARY DISORDERS

Introduction[1]

The effects of hereditary abnormalities on the central nervous system may be manifested as mental retardation, disturbances of neurological function, or psychiatric disorders. Where the abnormal heredity is confined to a single gene, or gene pair, it is, paradoxically, rather more common for two or three of these phenotypic disturbances to be seen than is true where more numerous and less well-defined genetic abnormalities are present. Thus Huntington's chorea and Wilson's disease generally produce neurological *and* psychiatric dysfunction, though a single dominant gene or a single pair of recessive ones, respectively, is the cause of each disease. Yet the poorly understood combinations of several genes which predispose to senile psychoses are not generally also associated with impairment of intellectual and neurologic function.

Mental retardation is by far the commonest hereditary disorder of the central nervous system associated with genetic abnormalities that are more or less well-defined biochemically. In phenylketonuria, maple syrup urine disease, homocystinuria, histidinemia, and galactosemia—to cite the best known of perhaps fifty nonchromosomal disorders—a specific block in

normal amino acid metabolism leads to the accumulation of sufficient amounts of intermediate compounds to be toxic to the brain. In other instances of mental retardation, such as the autosomal recessively transmitted Tay-Sachs disease, or the chromosomal abnormality associated with the cri-du-chat syndrome, there is little knowledge of the biochemical mechanisms involved.

Neurological dysfunction—alone or with other manifestations of CNS disorder—is characteristic of Huntington's chorea, Wilson's disease, familial or hereditary tremor, and the genetically heterogeneous group of congenital disorders, of which a number are hereditary, collectively diagnosed as cerebral palsy.

Both psychotic and nonpsychotic psychiatric disturbances may be seen in a number of hereditary disorders which are either well-defined syndromes, such as Huntington's chorea, or are the result of a complex interplay of hereditary endowment and environment, such as the senile psychoses. Both classes can be due, in large measure, to the indirect effects on the ego's functioning of a crippling or life-threatening disease, as discussed below under Wilson's disease. There is little doubt, however, that the specific and direct biochemical effects of a disorder, e.g., the accumulation of large and toxic excesses of copper in the brains of patients with Wilson's disease, can sufficiently derange brain function to produce psychiatric disorders.

Huntington's Chorea

Huntington's chorea is a widespread hereditary disorder of the CNS which is transmitted as an autosomal dominant and has an incidence of about four per 100,000 in Europe and the United States and about four per 1,000,000 in Japan. Clinical manifestation of the illness is rarely noted in childhood; the onset, generally, occurs between the fourth and sixth decades. Classically, chorea and the existence of the disease in members of previous generations of the patient's family are sufficient criteria for the diagnosis. Frequently, ". . . ataxia, dysarthria, dysphagia, dysphasia . . ." may be present; onset may occur in childhood; there may be, not uncommonly antedating peripheral neurological disturbances, . . amnesia, judgment, and/or orientation defects . . . ;" and there are almost always concomitant emotional disturbances including depression, with suicidal impulses, or a clinical picture indistinguishable from schizophrenia.

There is no biochemical knowledge of the disease; there is no chemical, clinical, or pathological test or finding which is diagnostic; and there is no specific treatment known. Except, possibly, for a test based on the administration of L-Dopa, diagnosis is made solely on clinical grounds and the physician is totally unable to tell if a child of a patient carries the dominant abnormal gene which causes the disease or is free of this abnormal allele, and will neither contract nor be able to transmit the disorder. Until diagnostic

clinical manifestations are noted, every such child has to be considered to have an even chance of possessing, or not possessing, the abnormal gene. Since signs and symptoms may not occur until the sixth decade, the problem of genetic counselling becomes difficult indeed.

Management of patients, once it is clear that Huntington's chorea is present, is limited to nonspecific chemotherapy, for both the neurological and psychiatric disturbances, and to supportive psychotherapy. Because of the physician's inability to diagnose the illness before clinical manifestations have appeared, the uncertainties that surround the individual and his relatives are almost as tragic as the effects of the disorder itself on the afflicted individual.

Wilson's Disease

Wilson's disease, with an incidence of about one in 200,000, is similar to Huntington's chorea in being hereditary (though transmitted in autosomal recessive fashion), in severely affecting the CNS, both neurologically and psychiatrically, and in not manifesting itself clinically early in life. In contrast, however, there is a great deal of biochemical information about the disease, diagnostic chemical tests can be applied, and specific therapy is available.

The etiologic agent causing the pathological changes which underlie the disease is copper, toxic excesses of which are accumulated in the CNS. Diagnosis is possible in the asymptomatic as well as the ill patient by the demonstration of a deficiency (less than 20 mg./100 ml. of serum) of the plasma copper-protein, ceruloplasmin, *and* an excess (greater than 250 *μg./*g. dry liver) of hepatic copper. Specific treatment consists of the administration of D-penicillamine, which removes copper from the symptomatic patient, in whom marked clinical improvement generally results, and from the asymptomatic one, in whom manifestations of the disease may be indefinitely prevented.

Almost all diets contain 2-5 mg. of copper and this amount is more than sufficient to supply the body's need for this essential element, which is present in a number of proteins such as cytochrome oxidase and tyrosinase. The total body content of copper is about 150 mg., and virtually none is lost in

the urine so that the normal individual excretes in his stools, principally from bile, almost precisely the amount absorbed from the diet. In Wilson's disease, a defect in the excretion of the absorbed copper has been inherited so that the metal accumulates slowly, but steadily, in the liver. Eventually destruction of hepatic parenchyma results in the release of relatively large amounts of copper to the blood whence it diffuses into the brain, the corneas (where it produces the diagnostic Kayser-Fleischer rings), the kidneys, and into almost every other tissue and organ. The toxic effects of copper in all these sites constitute Wilson's disease.

From this sequence it is apparent that copper first reaches toxic levels in the liver and, indeed, this organ almost invariably shows pathological changes by the time the diagnosis of Wilson's disease is first made even though the patient may be asymptomatic. Yet in only about 40 percent of patients who become symptomatic is the liver the source of the initial clinical manifestations of the disease. In another 30-40 percent neurological signs are first noted while neurotic, psychotic, or bizarre behavioral disorders herald the onset in perhaps 25 percent. Many patients suffer from significant psychiatric disturbance after an initial hepatic or neurological onset. Thus, in one group of twenty-two patients with Wilson's disease, nine, or 41 percent, had a psychiatric diagnosis of which three appeared to be psychotic.® Of forty-nine of our patients with Wilson's disease, thirty, or 61 percent, had significant psychiatric disturbances, of which nine were classified as

psychotic.

The emotional disturbances seen in these patients do not appear to be associated with significant mental retardation or impairment. (Emphasis on the intellectual impairment due to hereditary defects has probably tended to obscure the fact that more subtle forms of psychological disease can also be so caused.) Of the group of forty-nine patients just referred to, nineteen were evaluated on the Wechsler Adult Intelligence Scale (or the Wechsler Intelligence Scale for Children): individual IQ scores ranged from 57 to 135, with an average full-scale IQ for the group of 94.

Very few sophisticated psychiatric studies of patients with Wilson's disease have yet been made. Before the introduction of penicillamine, the hepatic and neurological disease, progressive and fatal, overshadowed the psychiatric illness. With the availability of effective chemotherapy, on the other hand, treatment—and prophylaxis—of hepatitis, tremors, and dysarthria have been so dramatically successful that recently attention has been given to investigating the frequent accompanying psychiatric disorder which is usually not life-threatening.

Beard, writing in 1959 before penicillamine was generally available, described a patient with indubitable Wilson's disease who also suffered from schizophrenia. He defined the latter as consisting of delusions of reference,

and hallucinations and affective flatness in a setting of clear consciousness without insight. Although he found a number of patients in the literature who were said to suffer from both Wilson's disease and schizophrenia, he considered the latter diagnosis generally to be incorrect, with the patients suffering instead from less well-defined ". . . confusional state(s) or dementia." This conclusion follows from Beard's assumption that schizophrenia is a specific illness developing in a patient with "... a schizoid personality or hereditary disposition . . . ," and he clearly differentiates the latter from the abnormal pair of genes which causes Wilson's disease.

In the relatively superficial psychiatric studies reported since, it is impossible either to describe a particular psychiatric syndrome specific for Wilson's disease or to differentiate the patients' manifestations from the psychiatric disorders seen in general practice. Six representative examples, selected from our patients, follow:

1. A middle-aged man spent the last ten years of his life in a (New York State) mental hospital, which he entered, before the diagnosis of Wilson's disease was made, with a diagnosis of paranoid schizophrenia.

2. A young man, of high intelligence and normal stability, suddenly began to suffer from, and act out, voyeuristic compulsions which soon led to his arrest, and a suicidal attempt while in jail.

3. An adolescent girl manifested neurotic disturbances to such a degree that psychoanalytic treatment was initiated. Within six years mild neurological abnormalities appeared and she became psychotically depressed and withdrawn.

4. An adolescent boy pushed a woman visitor into a swimming pool and chased his father with a shotgun before either neurological or hepatic abnormalities of Wilson's disease had become observable.

5. A married man in his early thirties attacked without warning an elevator operator in the belief that this man was threatening to kill his children.

6. A woman in her thirties had, over a period of about ten years, several alternating episodes of mania and depression which have required hospitalization in a state mental hospital.

Since 1960, the majority of patients with Wilson's disease have received regular therapy with penicillamine with marked clinical improvement which has, obviously, been particularly well documented with respect to hepatic and neurological disease. There is little doubt, however, in the minds of physicians who have treated more than one or two patients with this disease, that the psychiatric disorders also improve to a greater extent than would be expected in a similar group of patients without Wilson's disease. Although this is as

difficult to document as is the efficacy of any psychiatric therapy, the courses of the six patients described above are of some interest:

1. This man remained hospitalized and, despite intensive treatment to remove the excess copper, worsened progressively and died.

2. Life-long treatment with penicillamine, begun in 1960, was initially accompanied by weekly sessions of therapy with a psychiatrist which later were occasionally reinstituted for several months at a time. Neurological recovery from a state of near-incapacity has been complete. The patient has a wife and three children, effectively manages a moderately large and complex family business, and is active in civic and charitable activities.

3. Psychiatric and penicillamine treatment resulted in disappearance of the patient's mild neurological manifestations. A psychotic episode with depressive and schizophrenic overtones ended her marriage and required almost six months of hospitalization. Following discharge, treatment with penicillamine was accompanied by psychiatric treatment, chiefly involving a variety of tranquilizing and mood-elevating drugs. She married a second time, adopted a child and, despite continued immaturity, has managed to live a reasonably fulfilling life as a housewife in a city 1000 miles from her mother, on whom she remains quite dependent.

4. This boy, whose older untreated brother had died of Wilson's disease,

was treated with penicillamine and manifested no further psychiatric abnormalities. Mild neurological disabilities supervened before treatment was begun and these have persisted but produce no significant incapacity.

5. Treatment with penicillamine, and brief psychiatric hospitalization and treatment, have returned this man to a normal neurological and psychiatric state.

6. One further episode of mania and depression required hospitalization after regular treatment with penicillamine was instituted.

In the ensuing twelve years, however, only two episodes, requiring brief hospitalization, have interrupted her normal life.

These results, and the impression that ". . . the incidence of psychiatric disturbances is higher in patients with Wilson's disease than it is in the average neurological patient population . . ." make it difficult to escape the conclusion that the psychiatric abnormalities of Wilson's disease represent more than the reactions of a patient to a crippling and life-threatening disease. Such reactive emotional abnormalities are clearly part of the picture, but the toxic neurological effects which copper deposits can produce, the fact that there is ". . . widespread cortical damage . . . ," and the improvement in psychiatric dysfunction which follows removal of some of the excess copper, strongly suggest that too much of this metal can directly derange the

integrative functions of the brain.

Acute Intermittent Porphyria

The term “porphyria” is used to describe a number of disorders of porphyrin metabolism, some of which are inherited. Acute intermittent porphyria is the best known, the most intensively studied, and the form usually associated with psychiatric findings. The incidence of the disease, which probably occurs in all races, is around one in 5000. It is generally thought to be transmitted as an autosomal dominant. However, incidental and incomplete data which are given in two reports not primarily concerned with genetic aspects do not support this. They present no evidence of occurrence in successive generations, and they indicate an incidence in affected families of 22 and 20 percent when the propositus of each sibship is subtracted from its number of patients. These characteristics are more consonant with an autosomal recessive mode of inheritance than with a dominant mode, where one expects to find patients in successive generations and an incidence of 50 percent among sibs of affected families.

Acute intermittent porphyria is characterized by episodes of severe abdominal pain with nausea and vomiting. There may be accompanying fever and leukocytosis, and paresis or even paralysis of various muscle groups. Attacks may last for hours or days and are followed by long periods of good health. The ingestion of barbiturates—or perhaps other drugs—and acute infections are generally considered to be capable of precipitating attacks.

Biochemically the illness is associated with the excretion of porphobilinogen and its metabolic precursor, S-aminolevulinic acid, in the urine in amounts which may exceed 100 mg. daily. Because of the nonspecificity of the clinical picture a firm diagnosis should not be made unless these intermediates of heme biosynthesis can be demonstrated.

Acute intermittent porphyria has been considered by many authors to be characterized by psychiatric complications. Most commonly, these are thought to accompany the acute episodes with a ". . . complete return to clarity and reason . . ." when the attack subsides. The description of these manifestations varies from mild irritability or depression to delirium or frank psychosis. In a rather widely publicized paper in the British Medical Journal the episodic madness of King George III has been unequivocally attributed to acute intermittent porphyria. Presumably by referring his aberrant behavior to a genetically caused excess of porphobilinogen and 8-aminolevulinic acid rather than to unknown mechanisms these authors conclude that ". . . this diagnosis clears the House of Hanover of an hereditary taint of madness. . . ."

Unfortunately, the psychiatric investigation of this disease has been relatively naive and confined to conscious manifestations. Investigators have differed widely in their conclusions, as is implicit in a review of previous studies by Ackner, Cooper et al. The psychiatric disorders noted have been considered to be (1) a consequence of the inherited metabolic error, though

by unknown pathogenic mechanisms; (2) reactions to a recurrent but solely somatic disorder which the patients generally know to be life-threatening; (3) causative of the acute attack; or (4) coincidental findings. In the study by Ackner et al. the ". . . importance of emotional disturbances in precipitating acute attacks . . and the suggestion that the ". . . porphyric patient has a background of neurotic instability . . ." are not considered to be supported by the evidence in the literature. In their study of thirteen patients they could find no evidence for a psychogenic factor in the etiology of the disorder, nor for a neurotic predisposition. Although ". . . psychiatric symptoms commonly occur during an acute attack of porphyria .. . (they may) be largely psychogenic and unrelated to the underlying metabolic defect."

Clearly, treatment of the psychiatric manifestations which may accompany the acute attacks of porphyria is necessarily nonspecific. As noted, these disturbances subside when the attacks are over.

There are several other disturbances in porphyrin metabolism[2] which are inherited, but they have little or no association with psychiatric abnormalities.

Discussion

Wilson's disease, Huntington's chorea, and acute intermittent porphyria are similar in that each is caused by the inheritance of only one, or a pair of, abnormal genes. Their dissimilarities are greater than this shared characteristic. Thus, we know nothing of the biochemical defect caused by the abnormal gene of Huntington's chorea and have no chemical or pathological means of confirming the diagnosis, before or after the disease is clinically manifest; there is no effective treatment. There is no doubt that psychiatric disturbance is a major characteristic of the disease, but we do not know if the emotional disorder is a reaction to the somatic, neurological disease or is a direct result of the unknown biochemical defect, or is due to both.

We know at least the probable chemical locus of the biochemical defect which underlies acute intermittent porphyria—somewhere in the pathway of the biosynthesis of heme— but we know neither what the primary gene product—enzyme or protein—of the abnormal, or normal, gene is, nor how or if the abnormal amounts of porphobilinogen and 8-aminolevulinic acid produce the somatic symptoms of the acute attack. Unlike what appears to be true of Wilson's disease and perhaps Huntington's chorea, the available data leave quite uncertain whether the psychiatric manifestations which have been observed are in any way specifically related to the biochemical defect, or whether they solely constitute the reactions to a recurrent and life-

threatening illness.

Although we also do not know what the primary gene product of the "Wilson's disease gene," or its normal allele is, we have considerably more information about the etiology and pathogenesis of this disorder. The inborn metabolic error results in gradually increasing deposits of copper throughout the body, and the clinical manifestations of the disorder, very probably including to a significant degree the psychiatric disturbances, are the direct result of copper toxicity. In part, of course, the emotional abnormalities also represent reactions to a chronic disease which, untreated, is progressively disabling and ultimately fatal. Freud predicted, in 1920, that deeper molecular knowledge about psychiatric disease would make psychoanalytic techniques of treatment obsolete. His prediction is, to a modest degree, fulfilled by the unquestionable improvement, in the psychiatric disease of a significant number of patients with Wilson's disease, which accompanies the pharmacological removal of a portion of excess copper. Such improvement appears to be accelerated if psychotherapy, or nonspecific chemo-psychotherapy, or both, accompanies the life-long administration of d-penicillamine to remove copper.

These diseases are the only instances of hereditary psychosis about which we have any biochemical genetic knowledge. Unfortunately, they constitute an insignificant proportion of all psychiatric disease. There is little

doubt that heredity plays a significant, if not the dominant, role in the etiology of the psychoses, and of other psychiatric disturbance, but those causative effects are probably a summation of at least several synergistic genes. We have little knowledge about the linkages of these genes, the disorders associated with them, and no knowledge of the biochemical consequences of having inherited the normal or abnormal allele. Pick's disease is apparently associated with a dominant gene and, perhaps, Alzheimer's and Jakob-Creutzfeldt's presenile dementias have genetic determinants, but these vague bits of data are of little aid to diagnosis and of none to therapy.

Jervis summarizes our ignorance of these hereditary, emotional disorders: ". . . the precise nature of these genetic factors remains undetermined . . ." This ignorance includes for each such psychiatric disease, the number of genes involved as well as the structure, function, and concentration of their primary gene product and the manner in which the genetic endowment interacts with the individual's physical and emotional environment. At present, we have a significant part of such knowledge for only a few hereditary diseases of the CNS. In these, furthermore, psychosis is not the dominant clinical manifestation, and the primary interaction of the abnormal genes is with physical, not emotional, aspects of the environment. In phenylketonuria, galactosemia, the sphingolipidoses, and Wilson's disease the single-gene defect results in the accumulation of a normal chemical metabolite to concentrations which are toxic to the CNS. Just to speculate on

the number of genes possibly involved etiologically in schizophrenia, and how they may interact with the patient's emotional milieu, internal and external, is to make depressingly obvious how far we are from the time predicted by Freud fifty years ago: "the deficiencies in our description (of emotional disorders) would probably vanish if we were already in a position to replace the psychological terms by physiological or chemical ones . . . On the other hand it should be made quite clear that the uncertainty of our speculation has been greatly increased by the necessity for borrowing from the science of biology. Biology is truly a land of unlimited possibilities. We may expect it to give us the most surprising information and we cannot guess what answers it will return in a few dozen years to the questions we have put to it. They may be of a kind which will blow away the whole of our artificial structure of hypotheses." [pp. 82-83]

Genetic Terminology

Every inherited characteristic of a living organism is a consequence of a particular gene or of gene interaction. For some organisms, which are called "haploid", each characteristic is governed by unpaired genes; other organisms, including human beings, are termed "diploid" and possess a pair of genes for each characteristic, with one member of the pair derived from the father and the other from the mother. The number of genes in each human individual is unknown, but may approach 1,000,000.

A gene may be "autosomal," in which case it is present on one of the forty-four nonsex determining chromosomes; or it may be sex-linked, in which case it is located on the X chromosome. A gene is linked to other genes when all are present on the same chromosome, and are generally inherited as a unit.

A gene is termed "dominant" if the possession of one gene of a pair is sufficient to produce a specific disease, irrespective of the nature of its paired mate. A gene is "recessive" if both members of the pair must be abnormal for the disease to be produced. There are often two or more forms of a given gene, each of which is called an allele, and only one, or a pair, of which can be present in an individual. Where a disease-associated gene is recessive, the heterozygote, i.e., the individual with one abnormal and one normal allele, is called a "carrier" of the disease and, generally, does not manifest any clinical

abnormalities.

All genes function either by determining the structure of a protein, termed the “primary gene product,” or by regulating the rate and conditions under which the primary gene product is synthesized.

Inherited diseases may also be the consequence of the possession of more, or less, than the normal complement of forty-six chromosomes, or of abnormal forms of chromosomes. Such diseases are generally much more gross in their clinical effects than single-gene disorders for the obvious reason that a chromosome contains many genes.

Bibliography

Ackner, B., J. E. Cooper, C. H. Gray et al. "Acute Porphyria: A Neuropsychiatric and Biochemical Study." *J. Psychosom. Res.*, 6 (1961), 1-24.

Beard, A. W., "The Association of Hepatolenticular Degeneration with Schizophrenia," *Acta Psychiatr. Neurol. Scand.,* 34 (1959), 411-427.

Carney, M. W. P. "Hepatic Porphyria with Mental Symptoms," *Lancet,* 2 (1972), 100-101.

Freud, S. (1920) "Beyond the Pleasure Principle," in J. Strachey, ed., *Standard Edition,* Vol. 18, pp. 7-64. London: Hogarth, 1950.

Goldstein, N. P., J. C. Ewert, R. V. Randall et al. "Psychiatric Aspects of Wilson's Disease (Hepatolenticular Degeneration): Results of Psychometric Tests During Long-Term Therapy," *Am. J. Psychiatry,* 124 (1968), 1555-1561.

Jervis, G. A. "The Presenile Dementias," in *Mental Disorders in Later Life,* 2nd ed., pp. 262-288. Stanford: Stanford University Press, 1956.

Kallman, F. J. "The Genetics of Psychoses; An Analysis of 1232 Index Families," Congres International de Psychiatrie, VI. Genetique et Eugenique, pp. 1-40. Paris: Hermann, 1950.

Kallmann, F. J., L. Feingold, and E. Bondy. "Comparative Adaptational, Social, and Psychometric Data on the Life Histories of Senescent Twin Pairs," *Am. J. Human Genet.,* 3 (1951), 65-73.

Klawans, H. C., G. W. Paulson, and A. Barbeau. "Predictive Test for Huntington's Chorea," *Lancet,* 2 (1970), 1185-1186.

Lynch, H. T., W. L. Harlan, and J. S. Dyhrberg. "Subjective Perspective of a Family with Huntington's Chorea," *Arch. Gen. Psychiatry,* 27 (1972), 67-72.

Macalpine, I. and R. Hunter. "The 'Insanity' of King George III: A Classic Case of Porphyria," *Br. Med. J.,* 1 (1966), 65-71.

Scheinberg, I. H. and I. Sternlieb. “Wilson’s Disease,” *Ann. Rev. Med.,* 16 (1965), 119-134.

----. “Copper Metabolism and the Central Nervous System,” in O. Walaas, ed., *Molecular Basis of Some Aspects of Mental Activity,* Vol. 2, pp. 115-116. New York: Academic, 1967.

Scheinberg, I. H., I. Sternlieb, and J. Richman. “Characterization of the Psychiatric Manifestations of Wilson’s Disease,” in D. Bergsma, I. H. Scheinberg, and I. Sternlieb, eds., *Wilsons Disease,* Birth Defects Original Article Series, Vol. 4, no. 2, pp. 85-87. New York: The National Foundation—March of Dimes, 1968.

Slater, E. and V. Cowie. *The Genetics of Mental Disorders.* London: Oxford University Press, 1971.

Sternlieb, I. and I. H. Scheinberg. “Prevention of Wilson’s Disease in Asymptomatic Patients,” *N. Engl. J. Med.,* 278. 352-359.

Whittier, J. R. “Genetics in Psychiatric Practice,” *Eugenics Q.,* 5 (1958), 9-15.

----. “Clinical Aspects of Huntington’s Disease,” in A. Barbeau and J.-R. Brunette, eds., Progress in Neurogenetics. Proc. 2nd Int. Congr. of Neuro-Genetics and Neuro-Ophthalmology, World Fed. Neurol., Montreal, Sept., 1967. Vol. 1. *Huntington’s Disease,* pp. 632-644. Amsterdam: Excerpta Medica Foundation, 1969.

Whittier, J. R., G. Haydu, and J. Crawford. “Effect of Imipramine (Tofranil) on Depression and Hyperkinesia in Huntington’s Disease,” *Am. J. Psychiatry,* 118 (1961), 79.

Whittier, J. R., A. Heimler, and C. Korenyi. “The Psychiatrist and Huntington’s Disease (Chorea),” *Am. J. Psychiatry,* 128, 1546-1550.

World Health Organization Scientific Group. “Screening for Inborn Errors of Metabolism,” WHO Tech. Rep. Ser. no. 401. Geneva: WHO, 1968.

Notes

1 A section on the genetic terminology used in this chapter appears at the end.

2 Porphyria variegata, hereditary coproporphyria, erythropoietic porphyria, and erythropoietic protoporphyria.