

ROUGH DRAFT

Chemistry of Mental Disease

Address by Linus Pauling

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There are many kinds of mental disease, and many chemical aspects of mental disease. The human body, including the brain, which is the organ of thinking and memory, is composed of molecules. Vectors of disease are molecules or are composed of molecules. The genes seem to be molecules of deoxyribonucleic acid. The impact of the environment on a human being is by way of <sup>radiant energy or of</sup> molecules of chemical substances, ~~or radiant energy~~. Chemicals, called drugs, are used for the treatment and control of mental disease.

I shall not discuss the entire subject, chemistry and mental disease, for several reasons. First, I do not have time to do justice to the whole subject. Second, I do not know enough about the nature of the intermolecular interactions between the <sup>brain and the molecules of the</sup> many valuable drugs, such as chlorpromazine, now being used in the treatment and control of mental disease to present a sound and reasonable discussion of the mechanism of their action; I'm not sure that anybody knows enough. I shall accordingly not devote any time to this subject.

Some of the many types of mental disorder result from birth injury or environmental causes of a macroscopic character, which cannot be described as chemical. *I shall not discuss them.*

Temporary or permanent ~~brain~~ impairment of brain function may also result from ingestion of substances not normally present or normally present only in small amounts in the body. Among such substances are ethanol, compounds of heavy metals (mercury lead ~~to~~ "mad as a hatter"), and organic substances found in plants, such as LSD (lysergic acid diethylamide) and mescaline.

Chromosomal abnormalities, such as those resulting from nondisjunction, are a common cause of mental deficiency, and may possibly be involved in some cases of mental illness. Examples are Mongolism (extra chromosome number ~~21~~,

or other chromosomal abnormality), Turner's disease (XO), Klinefelter's disease (XXY, XXXY, XXXXY). *Trisomy of a D chromosome (13, 14, 15) or on E (16, 17, 18) give mental deficiency*

The incidence of Mongolism is about one in 600 births, that of Turner's disease about one in 900, and that of Klinefelter's disease about one in 400. *Rare, probably usually lethal!*

The abnormalities with little doubt result from the manufacture of enzymes in abnormal amount. It is usually considered that two genes of the same type manufacture twice as many molecules of the corresponding enzyme as one gene.

There may be exceptions, however. There is some evidence that the enzymes manufactures by the genes of the X chromosome are not present in twice the

*X*  
*X*  
*mm*  
*8*

amount in women as in men, and some evidence that one X chromosome in the cell remains extended, with its genes presumably active, whereas the other one (or more than one) rolls up, in such a way as to cut down on the gene activity. This rolled-up chromosome is presumably responsible for the Barr test.

Probably the major cause of both mental deficiency and mental illness is gene mutation. It is usually estimated that about half of ~~/~~ congenital defects in infants are of genetic origin.

An abnormal gene may fail to manufacture the molecules of enzyme for which the allelomorphic normal gene is responsible, or may manufacture abnormal molecules that are deficient in enzyme activity.

PKU

The most thoroughly investigated <sup>disease</sup> ~~case~~ of this sort is phenylketonuria.

The enzyme involved, located in the liver, catalyzes the oxidation of phenylalanine to tyrosine.

Phenylketonuria was discovered by Følling in Norway in 1934. It is transmitted by an autosomal recessive gene. The incidence in Europe and United States is one in 80 for carriers. About one percent of institutionalized defectives are phenylketonurics. Their mental defect is severe, with 80 percent of the patients having IQ less than 40. Neurological disturbances include an abnormal encephalogram, often with epileptiform seizures, hyper<sup>u</sup> activity,

poor attention span, and normal behavior.

There are few mental diseases that are as well understood as phenylketonuria. The cause of most mental disorders is unknown, and many are not well-defined, even from the clinical standpoint. It is probable that the mental deterioration that occurs in later life in patients with Huntingdon's Chorea is the result of a change in brain chemistry, the nature of which is not known at present. The deposition of copper in <sup>tissues of</sup> patients with Wilson's disease is without doubt responsible for the mental as well as <sup>the</sup> physical manifestations of the disease. A change in brain chemistry may well be responsible also for schizophrenia and other forms of mental illness.

Despite the present lack of knowledge, the possibility that many mental disease may have a molecular cause provides a powerful stimulus for research.

Recognition of a biochemical abnormality in a disease leads to a study of the <sup>molecular</sup> mechanism, ~~of the~~ a search for methods of treatment, and the hope that a cure will eventually be discovered.

In the California Institute of Technology work on the molecular basis of mental disease has been carried on for five years, at first with Dr. Richard Lippman as the principal investigator, and more recently by Dr. Kenneth N. F. Shaw, Dr. <sup>T.L.</sup> ~~Tom~~ Perry, and their collaborators. Associated with this work has been a study of mental deficiency in Hawaii, carried out largely by Dr. Elvira

Goettsch. This work has now been transferred to the University of Hawaii, with the President, Laurence Snyder, as the responsible investigator.

The work in the California Institute of Technology has been quite varied in nature. As an example of what has been and is being done, I may mention briefly the studies by Dr. Shaw and his collaborators on Hartnup disease.

This disease was first described by Dent and his coworkers in England in 1956. Four out of eight children are afflicted in the original Hartnup family. Fifteen cases in nine families have now been found, in England, Holland, and Germany. The parents in three families are blood relations.

The manifestations of the disease include a red scaly skin rash, sensitivity of the skin to sunlight, intermittent cerebellar ataxia that involves a lurching walk, jerky arm movement, and ~~an~~ tension tremor. The mental state ranges from normal to retarded and may include mild emotional instability, psychosis, delirium, ~~del~~usions, and hallucinations. These features are variable and episodic, and can be precipitated by infection or psychological stress.

A constant biochemical finding is a large excretion of certain amino acids.

Dr. Shaw obtained several Hartnup urine specimens from Dent's laboratory two years ago. Many amino acids are excreted <sup>in</sup> amounts ten times greater

than normal, but others are not affected. The amino aciduria is caused by defective reabsorption in the renal tubule.

Professor Dent had reported an abnormal metabolism of indole compounds, but Dr. Shaw found no such abnormality.

He was then successful in resolving this contradiction, by collaborative work with Professor Dent, in which a boy in the Hartnup family and a normal individual were given two grams of L-tryptophan by mouth, at first without and then with the antibiotic neomycin, also given by mouth, to prevent the growth of intestinal microorganisms.

Slide 1. Chromatogram of amino acids in normal urine.  
(10)

Slide 2. Chromatogram of amino acids in Hartnup urine (only half as much urine used). Note the great amounts of some amino acids.

Slide 3. (13). Urinary indoles after ingestion of tryptophan, both normal and Hartnup. The Hartnup urine contains much larger amounts of several indoles than the normal urine.

Slide 4. (16). The same, except that the antibiotic neomycin was given. Both subjects were also placed on a diet containing no plant materials in order to exclude exogenous indoles. It is seen that the excretion of indole compounds by the Hartnup patient was essentially normal.



Apparently the Hartnup abnormality involves an impaired permeability of the intestinal wall as well as of the renal tubule. This means that tryptophan and other amino acids from food remain longer in the intestine for metabolism by bacteria, converting them into indole compounds.

The impaired permeability of tissues in Hartnup disease may cause many chemical abnormalities--variable deficiency of tryptophan, partial deficiency of nicotinamide <sup>+ perhaps</sup> or other essential agents, possible toxic effects of metabolites produced by intestinal bacteria.

The treatment of Hartnup disease is simple--administration of a high protein diet and also nicotinamide. Possibly suppression of the growth of intestinal microorganisms by the use of neomycin would result in improvement.



The molecular diseases that lead to mental deficiency or mental illness have not been investigated thoroughly with respect to the nature of the molecular abnormality. The most thorough studies that have been carried out of molecular diseases are those of the hemoglobinemias, including sickle-cell anemia, and I shall present now a discussion of the present state of knowledge about these molecular diseases.

SLIDES. Patient cells }  
electroph. AA  
tactoids  
paper chromat.  
AA, AS etc  
SS etc  
Amino acid sequence V. Ingram  
Folding,  $\alpha$ -helix. Myoglobin. Kendrew  
Schweder

~~PKU~~, galactosemia, etc. - just mutations  
 hemophilia 1/50,000. Muscular dystrophy 1/20,000  
 Achondroplasia 1/5,000  
 Huntington's chorea 1/200,000

One of the striking features of the sickle-cell gene is its high incidence in certain populations. In some malarial regions in Africa as many as fifty percent of the people are sickle-cell heterozygotes.

MALARIA  
 OTHERS

The nature of the abnormality that causes its high incidence is now known.

It is protection against malaria. OTHERS

It is seen that there is a close relation between molecular disease and evolution. EVOLUTION

Life is a relationship among molecules, not a property of any one molecule.

So is therefore disease, which endangers life. (to next page)

But sickle gene too large  
 thalassemia

PKU (1/10,000)

cystic fibrosis (1 in 500 children)

schizophrenia (1 in ? (Europe))

~~Niemann Pick, Gaucher's, Tay-Sachs 1/8000 in Jews  
 vs 1/400,000 in others~~

~~maybe heterozygotes favored in crowded life?~~

Relation to evolution  
 Peptide patterns

150 mil yrs	18	horse &
11 mil. "	212	quill
8 vs 3	250 mil.	36
2 vs 3	560 mil.	