

# The Challenging Frontier-Part II: Current Research in the Field of Severe Childhood Mental Illness

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## Introduction

*This report is a supplement describing what has been happening in research within the past year in the area of infantile autism and childhood schizophrenia, severe disorders of communication and behavior and in related areas of neurology and genetics. This article will not duplicate but may enlarge upon work reported earlier in my paper, "The Challenging Frontier: Environmental, Genetic, Biochemical and Neurological Factors in Severe Mental Illness. \**

*The research summarized herein has been reported in newspapers and in medical and professional journals.*

A few months ago, newspapers across the country carried titles such as "Childhood Ill Laid to Brain," and "Autism is Physical, Not Environmental." Ritvo, Ornitz and coworkers at the UCLA Neuropsychiatric Institute, after 10 years of study, have published data indicating that "autism, a form of childhood mental illness, results from diseased nerve networks in the brain that filter information entering from the eyes, ears and other senses." For detailed information on this work see "The Challenging Frontier," pages 208-214.

The experiments of Ornitz and Ritvo support the theory that autistic children do not modulate or handle incoming auditory stimuli in a normal manner, at least not during rapid eye movement (REM) sleep. Autistic children *modulate the response in the same way that infants do*, and not as normal children and adults.

New research by Ritvo<sup>1</sup> has focused on possible neurochemical factors that might control sleep staging and be related to their central nervous system pathology. The biogenic amine, serotonin, regulates REM sleep in the brain stem centers. Serotonin is also present in the bloodstream where it is chemically bound within the blood platelets. In certain types of mental retardation

<sup>1</sup>SCHIZOPHRENIA 1:206-232, 1969.

such as mongolism and phenylketonuria, blood serotonin is *decreased*. (The importance of serotonin as a neural-transmitter is discussed in detail in "The Challenging Frontier," p. 215-220.)

In 1961, Schain and Freedman<sup>2</sup> reported *increased* levels of serotonin in certain autistic children. Ritvo has also found this true in autistic children, who have a significantly *higher* level of blood serotonin and a higher number of blood platelets.

In normal children there is a maturation-al factor whereby infants have high levels of serotonin. These levels decrease as children grow older. Ritvo states that there is also a significantly *greater variability of serotonin per platelet* and a greater variability of platelet levels within the youngest group of age-matched autistic patients (24-47 months). The researchers are now focusing on the differences in serotonin levels between those children with persistent elevations and those who are within the normal range, and why such variations are observed in autistic children.

Boullin, Coleman and O'Brien<sup>3</sup> have analyzed the serotonin (5-hydroxytrypta-mine) level in six children, aged 4 to 14, diagnosed unequivocally by Rimland<sup>4</sup> as having infantile autism. No patient had signs of organic brain disease. The researchers found that the serotonin uptake capacity was unchanged or increased in platelets from autistic subjects, while the platelets' ability to retain the amine was defective.

The uptake of serotonin and norepinephrine (biogenic neuron transmitters) by red blood cells and blood platelets in psychotic children has been studied in detail by Sankar.<sup>5</sup> He found that there were significant differences in the uptake of serotonin by the platelets in autistic children, schizophrenic children and children with character disorders. The lowest levels were found in autistic children and are compar-

able to normal children of a lower chronological age.

The differences in platelet properties between children with different psychiatric disorders may be due to differences in the membranes of the platelets, or in the metabolism of serotonin. Studies are underway to determine whether the uptake of serotonin by platelets is lower in schizophrenia due to a pathogenic mechanism including maturation, or metabolism of the serotonin. Sankar has also found that autistic children have a higher platelet count. There were no significant differences in the uptake of serotonin and norepinephrine by the red blood cells in any of the above psychiatric-disorders.

Since abnormal levels of serotonin have been found in mongoloid children, those children afflicted with phenylketonuria and in other types of mental disorder such as manic-depressive illness, one must be cautious in saying that autism is caused by a serotonin imbalance alone. Many other biochemical imbalances have been found in autistic children as well.

A study on the handicaps of autistic children has been made by Wing.<sup>6</sup> The development of behavior characteristics of autistic children was compared by parents of autistic, receptive aphasic, executive aphasic and partially blind/partially deaf handicapped children. Normal and mongoloid children served as controls. The comparison showed that autistic children are multiple handicapped, combining problems of comprehension and use of speech and right-left, up-down, back-front disorientations similar to those found in the congenital aphasic syndromes with abnormalities in the use of vision, difficulty in understanding gestures, abnormal body movements and preference for proximal senses as in congenitally partially blind-deaf children.

Barab<sup>7</sup> used different types of auditory stimuli, e.g., noise, non-noise, tonal and atonal music and the English and Danish languages in an experiment conducted to

measure the preference of autistic children for auditory material, hopefully to make certain tentative references about their receptive language abilities. English and Danish are for all practical purposes two identical stimuli except in one respect, *meaning*.

If the children understood English they would presumably choose English over Danish. If they did *not* understand English, then the two languages would sound alike, and children could not differentiate one language from another.

Autistic children of four to nine years of age, disturbed children, normal controls and two children with expressive-aphasia were tested. Buttons were pressed by the children to choose preferred auditory stimuli. Most of the autistic children were un-testable because their behavior was uncontrollable or because they could not distinguish between the basic noise/non-noise condition.

Of 17 autistic children only three could be used as subjects. Two of the three showed a preference for music, in the English vs music choice, while the third chose English over music.

All of the non-autistic subjects chose English over music; two of three showed a preference for English over Danish, as did the six controls.

*Not one* of the testable autistic children showed a preference for the English over Danish material, and neither seemed to be able to identify the English material, although it had been assumed for the most part that the children understood English. Thus in these limited tests, the autistic children did not seem to understand language of an extended or complex nature. Barab assumes that part of the problem has arisen in assuming that autistic children understand language. This view has been fostered by the stereotyped view of normal children withdrawing from a hostile environment as set forth by B. Bettelheim.

Further, autistic children can also be gaining much information from the tone and tempo of a person's speech, gestures, etc., leading one to believe that they understand language (English) more than they actually do.

Other studies of infantile autism have shown the following:

Treffert<sup>8</sup> noted that there were approximately 3.1 cases/1000 of children (under 12) afflicted with childhood schizophrenia and infantile autism in a Wisconsin study. The cases were divided into three classes:

- (A) Classic infantile autism.
- (B) Psychosis of childhood with later onset.
- (C) Psychosis complicated by demonstratable organicity.

Of these, 25% were in Group A, 57% in Group B and 18% in Group C. All groups had high male to female ratios, relatively low familial incidence of major mental illness, and a low incidence of prenatal and perinatal complications. Group differences seemed less compelling than the similarities and did not point to a difference in etiology between the disorders.

Hutt and Hutt<sup>9</sup> described the behavior of autistic children, dealing with "free field" behavior and their exploration of novelty. Simultaneous behavioral and EEG studies were made. Results led to the postulation of a neurophysiological hypothesis that children with infantile autism are in a *state of high physiological and behavioral arousal*. Results and implications of this work are discussed in the context of relevant evidence from animal studies.

Lockyer and Rutter<sup>10</sup> in a 5 to 15 year follow-up study of infantile psychosis found that infantile psychosis appeared to develop on the basis of a central disorder of language and of perception of sounds. Psychotic subjects were inferior to hospital controls in terms of social competence.

Szekely<sup>11</sup> observed 41 psychotic children

with no known organic damage, in an attempt to clarify certain aspects of psycho-pathology, which could be helpful in the etiologic classification of the syndrome of childhood schizophrenia. Two psychotic groups with apparently defective affect functioning are described. One seemed to be a primary and the other a secondary disorder, with different underlying pathology and prognostic expectations.

The first group showed hypersensitivity and intense inner emotional life, along with a defective ability to apply their emotions realistically to environmental stimuli. The second seemed to have a dull, subnormal potential for emotional functions and a consequently diminished interest (motivation) to participate in social life. The difference in the two groups might be compared with that of intellectual subnormality due to primary and secondary causes.

Many investigators have been trying to connect dreaming and rapid eye movement (REM) sleep with mental illness. All studies to date have been inconclusive as to whether schizophrenia is caused by deficiencies in REM sleep or related to "wideawake" dreaming.

### **Biochemical Studies of Autistic Children**

As noted in the "Challenging Frontier," new biochemical abnormalities continue to be discovered in mentally ill children and adults at an ever increasing pace. Celiac disease, resulting from an inability of the body to properly metabolize gluten, a wheat protein, found in bread and cereal, can cause eventual mental disorder if the patient is not put on a gluten-free diet. Several investigators have been studying celiac disease as relates to mental illness. Dohan<sup>12</sup> found that celiac disease was considerably more frequent among schizophrenic and autistic children and adults than in non-psychotic children. He also found that the

behavior of institutionalized schizophrenics improved considerably

when the patients were put on a cereal and gluten free diet.<sup>13</sup> Dr. Mary Stewart Goodwin whose work with the "talking typewriter" is well known, is currently studying celiac disease as it relates to mentally ill and autistic children.

Serum enzyme elevations of creatine kinase (CPK) and aldose activity<sup>14</sup> occur in *acutely* psychotic patients of all diagnostic categories. But these enzymes were *not* found to be elevated in autistic children, chronically psychotic patients or other non-psychotic patients. The serum enzymes were of the muscle type rather than of the cerebral or hepatic origin, which indicates a biochemical abnormality exists common to the acute psychoses, probably differing from that found in chronic schizophrenia and childhood autism.

Further evidence on biochemical causes of schizophrenia continues to mount rapidly. Himwich<sup>15</sup> reported hallucinations and delusions in schizophrenic patients upon administering two drugs. One drug, l-cysteine, is a natural amino acid found in the body. L-cysteine and tranylcypromine, a monoamine oxidase inhibitor, had *no* appreciable affect on normal volunteers. Yet in mentally ill patients, two mind affecting chemicals—N,N-dimethyltryptamine and bufotenin (a serotonin derivative)—showed up in the urine. They were assumed to have formed in the brain. This work further enhances the indoleamine biochemical theory of mental illness (see "The Challenging Frontier," p. 217).

Russian researchers<sup>16</sup> have related several biological features of the blood serum of schizophrenics to pathogenesis of the disease. Their data indicate that there is a biologically active factor in schizophrenic blood consisting of two components. The first produces changes in the electroencephalograph (EEG), is relatively stable, and is associated with clinical features specific for schizophrenia, while the other exerts an influence on evoked potential, is

unstable and is characteristic for schizophrenia as a whole, independent of its clinical variants. This data further supports the idea, that there is an important connection between schizophrenic blood serum and the manner in which the disease manifests itself.

Frohman<sup>17</sup> reports that the active fraction of schizophrenic serum contains alpha globulin (A2G) with a molecular weight near 400,000, plus a large number of fats. This serum exerts an influence on the permeability of the blood cell membranes, which leads to an increase of the neuron transmitters— $\gamma$ -aminobutyric acid and serotonin. It is suggested that this increase in the supply of these neuron transmitters in the nerve tissue is capable of *deranging cerebral nerve conduction*; leading to mental illness. Again, serotonin is implicated in mental disorders, as well as other neuron transmitters.

Pennell<sup>18</sup> suggests that the active fraction of this blood serum protein factor may include a carrier protein coupled with a relatively small molecule responsible for the biological effect. This low molecular weight component has an absorption spectrum typical of quinoline derivatives and resembles the phenylethylamine compounds which are known mind-bending drugs.

Hypoglycemia (low blood sugar) is very common in mental disorder and alcoholism. Lozovskii<sup>19</sup> has noted a biologically active component in the serum of schizophrenics which produces an inhibition of glucose oxidizing transformations and a rise of the lactate-pyruvate ratio.

Decreased "glycolipid"<sup>20</sup> concentrations have been found in certain areas of the brain of senile and schizophrenic patients. Decreased cholesterol was also noted in all areas of the schizophrenic and alcoholic brains.

A possible biochemical etiology for schiz-

ophrenia and manic-depressive psychosis which permits an explanation of the mode of action of antipsychotic phenothiazines and tricyclic antidepressants is described by Stein and Wise.<sup>21</sup>

The theory assumes:

(I) That a pathological gene leads to marked reduction in the activity of dopa mines-hydroxylase, the enzyme responsible for the conversion of dopamine to norepinephrine;

(II) that the resultant release of dopa mine from noradrenergic terminals of the reward system permits the formation, by autoxidation, of toxic quantities of 6-hydroxydopamine in the synaptic cleft;

(III) that continuous uptake of 6-hydroxydopamine over long periods damages the binding capacity and eventually, the structural integrity of the noradrenergic terminal;

(IV) that the resulting damage to the noradrenergic reward mechanism is responsible for the fundamental symptoms of schizophrenia and manic-depressive psychosis;

(V) that phenothiazines and tricyclic antidepressants exert their therapeutic action by blocking the entry of 6-hydroxy-dopamine into the noradrenergic nerve terminal.

*Trans*-3-methyl-2-hexenoic acid, isolated from the sweat of schizophrenics (see "The Challenging Frontier," p. 221), may be a metabolite of 6-hydroxy (or 2-hydroxy) dopamine. A similar destructive process involving 6-hydroxydopamine may be operative in Parkinson's disease. In this disorder, the normal resistance of dopamine neurons to the toxic action of endogenous 6-hydroxydopamine may be weakened after viral infection.

The mauve factor, a compound found in the urine of mentally ill patients has been identified as 2,4-dimethyl-3-ethylpyrrole. It was assumed to be a stimulant or hallucinogen.

It has now been shown by Sohler, et al.<sup>22</sup> to have a sedative effect. The compound may be formed by abnormal oxidation of an indoleamine in the schizophrenic patient.

Merlis<sup>23</sup> of Central Islip State Hospital also is looking for abnormal proteins in the blood serum of mentally ill patients. Already 30 proteins have been isolated from blood plasma by means of a technique known as disk electrophoresis (movement of particles in an electric field). Over 100 different human hemoglobins (red pigment in red blood cells) have been isolated, with the number expected to rise to 600. Some of these proteins may be responsible for creating chronic mental diseases of one type or another.

As research in the biochemical abnormalities of mental illness continues to accelerate, more mental disorders will be identified and treatment or cures found at an ever increasing rate. Already "miracle drugs" such as the phenothiazines have brought new hope to large numbers of mentally ill patients and children. The list of mental disorders and illness helped by chemotherapy and diet continues to grow.

A recently released drug<sup>24</sup> of a new generic type may be superior to the phenothiazines, in that it will have antipsychotic effects without the adverse side effects of the thiazines such as sedation and tremors. It is a primozide, a diphenylbutapiperidine. It may block the effect of dopamine which has been implicated in schizophrenia.

The role of body chemistry and its contribution to learning disorders and behavior in children is summarized in a recent book, *The Schizophrenias, Yours and Mine*.<sup>25</sup>

#### Treatment of Infantile Autism and/or Childhood Schizophrenia

At the present time, one of the most promising methods of treating disturbed children via chemotherapy has been in-

vestigated systematically by Rimland.<sup>26</sup> In a national study started over two years ago, (in which many autistic children of NSAC\* parents participated), it was found that over 40% of disturbed children were significantly helped by megadose vitamin therapy consisting of vitamin C (ascorbic acid) and the B vitamins, especially B<sub>3</sub> (niacinamide). The children are not cured in any sense of the word but their condition is improved.

Rimland has recently reported that certain children who were on *both* vitamins and Dilantin (an antiepileptic drug) improved quite remarkably. Megadose vitamin therapy has been used for years and has proven successful in treating several types of illness.

Osmond, Hoffer,<sup>27</sup> Rimland, Rosenberg<sup>28</sup> and many other researchers have gotten excellent results although controversy still exists over the effectiveness of the vitamins.

More recently, Linus Pauling (a Nobel Prize winner) has been expounding the virtues of vitamin C as prevention and treatment for the common cold.

Dilantin<sup>29</sup> has been used for over 30 years as an anticonvulsant and more recently, with excellent results, to modify the behavior of depressed patients, emotionally disturbed children and children with serious behavior problems. Most interestingly, Dilantin has changed the behavior of hardened criminals from aggressive and violent to agreeable and cooperative. Both the vitamins and Dilantin are perfectly safe when used under a physician's care.

For years certain children have been more than unusually restless, noisy, destructive and distractible. In school, these children have difficulty learning, are antisocial and become severe discipline problems and delinquents. Their behavior appears to be a distinct disease syndrome that is inborn. These youngsters, called hyperactive or hyperkinetic, have caused untold distress

\* National Society for Autistic Children

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among parents, teachers, doctors and everyone who comes in contact with them. The "hyperactivity syndrome" has been noted in brain damaged (oxygen deficiency, encephalitis, etc.) and emotionally disturbed children.

It is not confined to children alone. Stewart<sup>30</sup> describes in detail the symptoms of this disorder identified over a century ago. He noted that certain children start life with a distinctly abnormal temperament, which appeared to be present in 4% of suburban grade school children of middle class families. The hyperkinetic syndrome is much more common in boys than girls, the ratio being six to one! Thus, it again appears that some inherited eccentricities of behavior or learning may be sex-linked.

The idea that hyperactivity has a biological basis in fact is further strengthened by the dramatic change toward desirable behavior produced in these children by stimulating drugs such as the amphetamines and methylphenidate (Ritalin). Under their influence, the hyperactive child, in 50% of the cases, becomes quieter, exhibits a longer attention span, performs better in school and is easier to get along with. Amphetamines act on the reticular formation in the brain stem and also on the metabolism of neuron transmitters such as norepinephrine (noradrenalin).

Recently much controversy has arisen over the use of amphetamines in treatment of the hyperkinetic child. Under the care of a physician there is no danger. Only when drug addicts or people on dangerous weight reducing programs take *massive* doses of the amphetamines (also called "speed") can trouble be expected. The "hyperactive" syndrome is another example of a psychogenic disorder which has a physical basis in fact and can be transmitted from parent to child. See "The Challenging Frontier," p. 220, for a description

of the "anxiety neurosis," caused by an excess of lactic acid in the blood. This neurosis was formerly believed to be strictly psychological in origin.

Modifications of operant conditioning, also known as behavior modification or reinforcement therapy, continue to show the most promise for teaching severely disturbed and autistic children. The technique is also effective with the severely retarded and multiple handicapped child. Parents, psychologists, teachers and psychiatrists are having moderate to remarkable success with two-thirds of the children studied. The techniques have swung away from physical punishment. It has now been replaced with firm but gentle restraint, distraction, disregard of undesirable behavior, etc. Slapping, shocking or withholding food to famished children as practiced in the early days is passe.

Halpern<sup>31</sup> describes a successful small group approach in language training of young autistic children with limited communicative powers ranging to mutism. The program was built around a *highly structured* environment. The schedule involved greeting, names, the day, daily weather, etc. followed by a series of lotto games designed to teach auditory and visual word recognition and to present replicable models for interaction in a predictable relationship with an adult. Free play in an outside play yard, followed by rest, a music period and a snack completed the two hour daily session. Early follow-up findings of these children after four years showed 73% in public school (most in special classes) with the remainder in residential treatment centers. This is a more promising result than had previously been deemed possible.

Studies of autistic children have been appearing more frequently in the literature as interest, research and techniques for helping these children are expanded. These reports comment favorably upon the progress of the children. Hartung<sup>32</sup> reviews procedures to increase verbal imitative skills and functional speech in autistic children.



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He discusses the importance of establishing verbal behavior. Theoretical foundations underlying verbal conditioning are noted and procedures and related theoretical implications are reviewed in detail. A behavior strategy for language training of a child with autistic behaviors is demonstrated by Sulzbacher and Costello.<sup>33</sup>

Marshall, et al.,<sup>34</sup> describes the goals and procedures of a communication therapy program for autistic, mentally retarded children using operant conditioning, via a team approach.

Dagomi-Weimberg<sup>35</sup> reports on the successful language development of an autistic non-speaking child from mutism, echolalia and broken language to normal speech, accompanied by social improvement.

### The Origins of Schizophrenia

The importance of genetic factors in the development of schizophrenia has been established beyond doubt, although it is clear that environment can play its etiologic role in many types of mental disorder (see "The Challenging Frontier," p. 223-224). A review by Heston<sup>36</sup> states that relatives of schizophrenics have shown a high incidence of schizoid behavior.

Schizoid means schizophrenic-like disabilities, which are usually much less severe than schizophrenia and do not prevent the

subject from earning a living. About 45% of the relatives (sibs, parents and children) of a schizophrenic are schizoid or schizophrenic, while 66% of the offspring of two schizophrenics are ill. From the known risk of schizophrenia it is estimated that about 4% of the population will be afflicted with schizoid and schizophrenic disease as contrasted to 1% of the population who will have schizophrenia.

These statistics are most readily explained by the hypothesis that a defect in a single autosomal, dominant gene accounts for the genetic contribution to both schizoid and schizophrenic disease (the dominant gene hypothesis) and that most schizoidia-schizophrenia is associated with defects in a single basic biochemical or physiological pathway transmitted by a single mode of inheritance.

Other researchers believe that many genes are involved in causing schizophrenia (polygenic theories), for in view of all of the degrees and types of mental illness and large number of biochemical abnormalities found in the same mentally ill, autistic or schizophrenic patient, the polygenic theory also makes sense, since each biochemical defect is usually associated with a single defective gene.

Research on the etiology (cause) of schizophrenia has taken many approaches. The technique which appears to have the least number of objections is called the "high risk method" and involves studying the offspring of schizophrenics before problems arise. Thus, the adverse effects of institutionalism, drugs, follow-up, etc. are minimized. A most complete (to 1967) and unbiased summary on causes of schizophrenia is outlined in "The Origins of Schizophrenia,"<sup>37</sup> an account of the Proceedings of the First Rochester International Conference on Schizophrenia. In these proceedings, hereditary and socio-cultural factors, psychological and physiological data and one biochemical abnormality are presented.

Data which indicates that schizophrenic



and autistic children are suffering from an organic disease is noted by Goldfarb<sup>38</sup> in this summary. Schizophrenic children as a group showed a very high incidence of congenital stigmata and, even more significantly, of *impaired neurological function*.

The stigmata included hair whorls, high palate, abnormal head size, ears, teeth, tongue, palm, finger prints, hand creases and toes. Large numbers of these children had more than one stigmata—often five. Preliminary data also indicates that fine ridge disturbances in the fingerprints may also be characteristic of schizophrenic children. (Mongoloids and children with severe defects often have abnormal palm prints.)

Central nervous system disorders manifested by abnormal reflexes and reflex changes, manifest motor and sensory dysfunctions and abnormal electroencephalographs also were present. On this basis, 65% of the schizophrenic children were classified as having a definite impairment of the central nervous system (CNS). Soft signs of neurological impairment included disturbances of gait, posture, balance, coordination, muscle tone, perception and speech. In a neurological study of 48 public school children, no children had unequivocally diagnosed impairment of the CNS and "soft" signs were noted in only two children.

Goldfarb divided the schizophrenic children into two groups depending upon the positive neurological signs, e.g., CNS and "soft" signs—the "organic" group; and no signs—the "non-organic" group. The majority of "organic" children functioned at defective levels of intelligence while the "non-organic" children functioned at average levels or higher. Virtually all of the mute, very bizarre children termed autistic showed signs of neurological impairment and are included in the "organic" group.

Interestingly, although mothers have been blamed in the past for causing schizophrenia in

their children due to rejection, etc., Goldfarb found that 38% of the mothers of the organic group (or severely impaired children) showed *higher clarity of communication that the highest clarity score obtained by any mother of "non-organic" children*. Children who showed no signs of impairment of the CNS came from families which were more consistently deviant in psychosocial functioning than those of the organic schizophrenic children. Excluding the severely impaired "organic" children, the moderately severe "organic" children with intact families *improved equally* well in psychiatric status in day or resident programs. By contrast, most of the "non-organic" children showed improvement in residence while *none* did so in day care programs. Parallel data was obtained by DeMeyer (see "The Challenging Frontier," p. 228) when she noted that the most severely disturbed psychotic children came from the admittedly better homes, while the non-psychotic children came from the worst environment.

In a book titled "*Brain Damage in Children—The Biological and Social Aspects*"<sup>39</sup> almost all of the symptoms present in brain damaged children are present to varying degrees in mentally ill and emotionally disturbed children. An excellent complete (to 1964) bibliography on the subject of brain damage dealing with its description, diagnosis, etiology, treatment, education and management is given in this book and could well be applied to most disturbed children.

#### **Related Medical Studies in the Fields of Mental Retardation, Genetics, etc.**

At the present time, no one yet knows the etiology or etiologies of infantile autism although many biochemical and physical abnormalities have been found in such children. Within the past 10 years biochemical research already has uncovered the cause of over 60 *genetic disorders*.<sup>\*0</sup> Several of the defects display symptoms similar to those of infantile autism. A new metabolic disorder is being identified almost every

month. In each case, these disorders are caused by a defective or missing gene which causes a faulty enzymatic reaction to occur in the body. In more than half these genetic diseases with known enzymatic defects, severe mental retardation and mental disorder results. The most well-known biochemical disorder is phenylketonuria (PKU). Detection of this disease in new born babies via a urine test is now mandated in several of our states. More recently Tay-Sachs disease<sup>41</sup> has received a great deal of publicity. Tay-Sachs disease is a fatal disorder of early childhood resulting from the body's inability to break down certain fats building up in nerve cell tissues so that the cells eventually burst.

Most metabolic disorders<sup>40,42</sup> result from the body's inability to properly metabolize amino acids, sugars and fats (lipids) found in our normal diet. Several types of metabolic disorders are treatable with vitamins. It is also possible to modify the effects of some of these disorders by removing the offending substance from the diet of the new born. Yet in spite of the fact that we have identified 200-250 defects resulting in mental retardation, about 75% of the causes of mental retardation still remain unknown!

Now that man is capable of detecting severe genetic abnormalities, much can be done in the future to modify or prevent their devastating effects. Control of diet has been mentioned. Biochemical geneticists<sup>43</sup> are looking at the possibility of a more fundamental approach, namely the act of transplanting the missing genes themselves or modifying their structures, but this technique is unlikely in the immediate future. Or donor cells which contain the missing genes might be implanted into a baby born without them. This is already possible in certain types of anemia<sup>44</sup> in mice.

Man has recently succeeded in identifying, synthesizing and isolating biochemicals of fantastic complexity, a feat which staggers the

imagination of a professional chemist. In 1969, Edelman,<sup>45</sup> a physician and molecular biologist, led the team which put together a gamma globulin, an antibody, which is one of the basic defenders against disease in the higher forms of life. Before rubella vaccine became available, gamma globulin was often given to mothers exposed to German measles to give rapid, but temporary immunity to the virus.

Within the past year, an enzyme, ribonuclease, has been synthesized by two groups of researchers working independently of each other. One group at Rockefeller University was headed by Merrifield and Gutte,<sup>46</sup> the other at Merck Laboratories by Denkwalter and Herschman. Ribonucleic (RNA) and deoxyribonucleic acid (DNA) are fundamental building blocks that determine the nature of all living things— whether they will grow normally or abnormally, or whether they will reproduce their kind or perish. Ribonuclease is the enzyme (or catalyst) necessary for their biochemical activity. Although it is a small molecule as enzymes go, its synthesis shows that man is coming ever closer to his goal of emulating nature at the most basic biochemical level.

Scientists at Purdue<sup>47</sup> have partly unravelled the structure of an even more complex intracellular enzyme, "lactate dehydrogenase," involved in the vital body process of breaking down glucose (sugar) and generating energy. It consists of four subunits, has a molecular weight of 140,000 and contains over 310 amino acid positions in a new and unique structure. In the future, man will undoubtedly synthesize enzymes which are lacking in the body and use them as chemotherapeutic agents to rectify inborn errors of metabolism like PKU.

Most recently Li<sup>48</sup> and coworkers have succeeded in synthesizing one of the pituitary glands' most important hormones, somatotropin or human growth hormone

(HGH). Analysis shows HGH to be a very complex molecule with a chain of 188 amino acids containing two loops in a three dimensional structure. It is the biggest protein made to date. HGH controls not only growth, but has a profound influence on important bodily functions, including the metabolism of sugar, fats and proteins and the production of sex hormones. It has proven of great value in treatment of dwarfism and other pituitary deficiencies.

Unusual antibodies are being found in chemical studies of blood and cerebrospinal fluid from multiple sclerosis (MS) patients.<sup>49</sup> These antibodies are believed responsible for causing MS by attacking nerve sheaths and destroying them. Heath has proposed a similar immunologic disorder as a cause for schizophrenia. Other investigators have noted abnormal antibodies in the blood serum and brains of acute schizophrenic patients (see "The Challenging Frontier," p. 218-221).

Another exciting advance has been made within the past year. An actual gene has been finally isolated by Harvard scientists.<sup>50</sup> This gene, from a common intestinal bacterium, controls the enzyme which enables the bacterium to metabolize lactose, a sugar which is converted into energy. The isolation of this gene is the first giant step toward man's control of heredity.

### Studies of Brain Structure and Function

The study of the organization of the brain is opening up a new field of exploration having to do with brain structure and how it is involved in complex forms of behavior.<sup>51</sup> The sensory and motor centers have been known for years but make up only a small part of the brain area.

This new field of study called *neuropsychology* is pin-pointing areas of brain lesions and injuries responsible for specific behavioral disorders and should enable one to better understand the more complex functions such as

speech, writing, mental disorder, etc.

Destruction of the cortex of the brain, which includes the brain stem and reticular formation (first area, or lower rear and base of the brain), results in pathological states. There is a marked deterioration of wakefulness, unconsciousness results, memory traces become disorganized, the brain cannot discriminate among stimuli, and marked changes in behavior occur which are pathological.

The second area of the brain (upper rear) plays a decisive role in the analysis, coding and storage of information. In this area a primary zone sorts and records sensory information, a secondary zone organizes and codes it and a third zone lays the ground work for organization of behavior. Injuries or lesions in this area lead to a disorganization of all senses and behavior.

The third part or frontal lobes of the brain serve primarily to activate the brain and regulate attention and concentration. All areas appear to be interrelated to each other and lesions in different zones give rise to different behavioral aberrations.

Geschwind<sup>52</sup> has described the different types of aphasia (disorders of language resulting from damage to the brain) and related these disorders to the area of the brain involved. Damage to the frontal lobes (Broca's aphasia) produces little speech which is emitted slowly, with great effort, poor articulation and with small grammatical errors. But these patients comprehend the spoken and written language normally and can sing a melody correctly. With damage to the left temporal lobe (Wernicke's aphasia) speech is effortless and normal, but empty and disorganized and conveys little or no information. This type of aphasia results in a patient being able to form good letters but writing is also disorganized and meaningless.

These two brain centers are connected by an area called the "corpus callosum" and lesions in this area cause other unusual

types of aphasia. A syndrome called "isolation of the speech area," appears similar to many speech characteristics of infantile autism.

The injured patient shows no language comprehension in the ordinary sense, and never utters propositional speech but can *repeat* words, sentences and phrases perfectly with normal articulation, can complete sentences started by the examiner, and is capable of verbal learning and can sing correctly. Upon autopsy, the classical speech area including Wernicke's and Bro-ca's area were intact, as were the auditory inflow pathways and the motor outflow pathway for the speech organs.

In the regions surrounding the speech area the tissue was destroyed and the speech area isolated so that the language areas and speech areas were disconnected. On the other hand, the intactness of the speech region and its internal connections insured correct repetition, and the preservation of verbal learning in the undamaged hippocampal region involved in learning was intact and probably accounted for the remarkable ability to carry on the memorizing of verbal material.

The more that we learn about the brain and the organization of language, the more obvious it becomes that speech patterns of autistic children can not possibly be caused by a faulty environment as stated by Bet-telheim in his book, "*The Empty Fortress*."

In both monkey and human infants subjected to brain damage from asphyxia<sup>53</sup> (lack of oxygen) at birth, handicaps that arise from lack of oxygen had appeared to disappear with time. Recent brain studies have shown that this is not the case.

In experiments with rhesus monkeys, various levels of asphyxia were obtained ranging from 4 to 21 minutes. The monkeys were sacrificed at various stages in their life. Their behavior, neurological functions and brain tissue were studied in detail. In monkeys asphyxiated for eight minutes or more, at which point

resuscitation becomes necessary, parts of the brain had been destroyed leaving pitted cavities or areas which had atrophied, particularly in the thalamus, midbrain and brain stem. Monkeys whose brain showed these abnormalities upon autopsy, showed abnormal neurological signs at birth, e.g., lack of coordination, weak cries, seizures, etc.

Monkeys who appeared perfectly normal in appearance in later life were dull, slow, inactive, uncoordinated, had peculiarities of locomotion and showed a memory defect. Upon sacrificing, these monkeys still showed sunken scars and cavities in the brain. It is assumed that similar damage has occurred in the brains of human babies who have been resuscitated at birth after eight minutes. After 12 minutes asphyxiation, symptoms similar to human cerebral palsy and severe brain damage with mental retardation appeared.

Towbin<sup>54</sup> has studied brain damage upon autopsy in the human fetus and in premature and full term infants. He has related this damage to mental retardation, cerebral palsy and central nervous system disease such as epilepsy and behavioral disorders. Atrophied and dead germinal tissue was observed in the deep cortical area of the brain.

A correlation was found between the corresponding location and type of the lesion caused by hypoxia (lack of oxygen), its time of occurrence and the resulting mental retardation and cerebral palsy.

The deeply rooted concept attributing organic mental retardation and cerebral palsy to birth injury appears to be in error to a significant degree. For in a major portion of the cases of hypoxic brain damage studied, early fetal brain tissue and structures had been *damaged weeks or months prior to delivery*. This accounts for the frequent occurrence of organic mental retardation and cerebral palsy in children with uncomplicated deliveries.

**Miscellaneous**

New evidence that medical x-rays used to diagnose illness can cause a startling increase in the number of mentally retarded and deformed babies was recently revealed by Uchida.<sup>55</sup> After abdominal x-rays taken at *any time* in their life, women had *eight* times as many mentally defective mongoloid children as women who had never been x-rayed, and *ten* times as many children with birth defects.

The enigma of cot death or sudden infant death (SID) among apparently healthy children has been the subject of extensive bacteriological, virological, immunological and biochemical study with no definite conclusions as to cause of death. Weinberg and Purdy<sup>50</sup> found that over 90% of the SID subjects had abnormal chromosomes involving from 40 to 80% of the cells and showing from one to four defects per cell. Chromosomal abnormalities<sup>7</sup> are usually found in only 0.5% of the general population. Dermatoglyphics (study of palm prints) showed a high proportion (29%) of abnormal simian lines in SID children as compared to 3% of the general population. The above abnormalities are most frequently associated with drugs, irradiation and viral infections. The abnormal chromosomes are probably caused by an undetected intrauterine infection of unknown origin or dormant viral infections which becomes active in early life, causing SID in infants.

In the past, several studies of the chromosomes of mentally ill children and adults had shown *no visible defect* (see "The Challenging Frontier," p. 225). Most recently, Sankar<sup>58</sup> has noted extensive chromosome *breakage* in the leucocytes (white blood cells) of children (ages 3-12) affected with infantile autism.

Of the 67 children studied, 18 were diagnosed as psychotic, 9 had primary behavior disorders, 18 were non-autistic schizophrenics, and 31

were autistic-schizophrenics. None of the children had any significant aneuploidy (abnormal chromosomes) or mosaicism (mixtures of chromosomes). Out of 18 schizophrenic children, 10 had no breaks while 6 had 1% breaks. Similar proportions of breaks were noted in the children with psychosis and primary behavior disorders. By contrast, in the 31 autistic children, only 3 had no breaks, whereas 6 had 1% breaks and 22 had more than 1% breaks including 4 who had 5% or more breaks.

In previous studies Sankar has shown that the autistic child differs markedly from the non-autistic child in many biochemical parameters (see "The Challenging Frontier," p. 219-220).

Sankar states that "Biochemical studies coupled with these chromosome studies indicate that autism is an extensive pathological disorder. The schizophrenia in these children may be thought of as being associated with a *high level of organic disturbance and damage to the neurobiological substrate.*

"The psychiatric defect in these autistic children may be only one by-product of a syndrome of neurobiological damage, which may be due to defects of embryonic maturation and intrauterine damage, irrespective of genetically-determined defects or to genetically determined hereditary mechanisms. This genetically-determined damage may be monogenic or polygenic. One may wonder whether infantile autism as a nosological entity is best classified as a psychiatric illness. More detailed studies are needed before this hypothesis can be advanced with greater certainty."

**Genetics and Prediction of Gross Defects in Unborn Children**

Chromosomes are rod-like structures that occur in the nucleus of every cell. Within the chromosomes are the genes which determine the hereditary characteristic of an

organism. The genes are composed of long chains of DNA protein molecules that directly control a cell's biochemistry and inherited characteristics. In each human cell there are 24 chromosomes. Twenty-two are autosomes (grouped A-1 through G-22) and two are the sex chromosomes, X and Y. Normal males contain one X and one Y chromosome and females two X chromosomes.

In about 0.5% of the general population, there are chromosomal defects which can cause mild or devastating consequences to man. The most widely publicized chromosomal defect is the extra chromosome associated with mongolism, also called Trisomy 21 or Down's syndrome. Other trisomies of the autosomes result in gross physical and mental defects.

Other defects involve extra or missing sex chromosomes. An example of such a defect is the XYY syndrome. Recently publicized is the fact that a large number of mentally dull or retarded, aggressive, tall males commit violent crimes and are found in large numbers in prisons and mental hospitals (see "The Challenging Frontier," p. 224). There are over 40 known defects of the sex chromosomes alone. More than half can cause dullness or retardation, sterility, inborn homosexuality, gross physical defects, etc.

In spontaneously aborted fetuses, between 25% to 35% have gross chromosomal abnormalities resulting in severely deformed babies which can not survive. Usually nature causes these fetuses to abort early. Occasionally they will survive to birth and die shortly thereafter or in early life.

For the last several years a chromosome analysis was determined by means of a Karotype (a chromosome blueprint) obtained from blood, bone or skin tissues. In the past few years a technique called "amniocentesis" has come into its own. The amniotic fluid surrounding the fetus

is withdrawn through the abdomen with a hypodermic needle and this fluid analyzed for abnormal chromosomes and chemicals. Amniotic taps have been used to detect and manage Rh-factor pregnancies. Amniotic fluid diagnosis has lowered the infant Rh disease rate from 25% to 2%.

The amniotic fluid contains a wealth of information about the unborn baby who sheds skin cells in it, swallows it and urinates in it, leaving a biochemical and chromosomal trail. By analyzing the baby's chromosomes, doctors can identify a mongoloid or chromosomally defective fetus at about three months of pregnancy. But the most widespread potential for amniocentesis lies in the ability to eventually predict more than 1,500 genetic diseases which cause one out of every five childhood deaths.

The detection of fatal Tay-Sachs disease<sup>59</sup> mentioned earlier can be determined by looking for the absence of an enzyme in the amniotic fluid by means of chemical tests. If the developing fetus has fatal Tay-Sachs disease, doctors and parents can decide whether or not to abort the child, saving the parents from the heart break of having a doomed child. Around 30 genetic-defects can now be picked up by amniocentesis.

By the same token, chromosomal analysis of the fetal fluid can predict with 100% certainty whether the fetus is a mongoloid, a severely defective retarded child with extra autosomal chromosomes or has abnormal sex chromosomes. If state law and religion permit it, early abortion can be performed. Or parents who carry a defective gene (and can now be identified as carriers) perhaps can be discouraged from having children of their own when the risk is great.

In view of all of the major advances in the field of biochemistry, neurology, genetics, chemotherapy and educational

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techniques, the time is not too far distant when the cause or causes of infantile autism and childhood schizophrenia will be positively identified and treatment found for these disorders.

The evidence is so overwhelmingly in favor of a biochemical and/or neurological defect, as the causative factor in infantile autism that

parents should no longer feel guilty or believe that they caused the child's condition.

And professionals in the mental health field should offer as much sympathy, help and understanding to the patients and families of those afflicted with severe mental and behavioral disorders as is now accorded those with severe physical defects.

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