THE EPIDEMIOLOGY OF MENTAL DISORDER ASSOCIATED WITH DAMAGE TO THE BRAIN AFTER BIRTH

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IN our current stage of knowledge and ignorance of the etiology of mental disease, those factors which are known to be associated with brain damage offer a fruitful field for epidemiologic study. While good evidence exists that such damage can cause behavioral disorders, there is still great need for clear cut explanations of the relationships between the cerebral pathology, its presumed etiologic background and its dependence upon a number of ill-defined associated factors. The voluminous literature on the subject offers some facts and many hypotheses, but few complete pictures. There is a great need for well-planned, well-controlled, incidence-measuring, prospective studies. This present summary will discuss a few of the most promising leads under the general titles of jaundice, anoxia, trauma, poisons, infections, deficiency diseases, convulsive disorders and cerebrovascular disease. It will be concerned essentially with those conditions which produce permanent brain damage as distinct from those associated with an acute and reversible disorder not resulting in chronic cerebral pathology.

JAUNDICE

Although it is believed that one per cent of institutionalized mental defectives suffer from kernicterus (31) the exact cause of high serum bilirubin in each specific case is not known. Two mechanisms appear to be of significance—the blood group incompatibility between mother and fetus which leads to continued red cell destruction after birth (39) and the immaturity of the liver of some neonates which prevent the proper conjugation and detoxification of the indirect acting bilirubin to the non-toxic, direct acting form (34). It is known that the proximate cause of kernicterus is the high level of serum indirect

acting bilirubin which is dangerous at levels over 30 mg. per cent and possibly hazardous at levels over 20 mg. per cent (13). Since bilirubin levels can rise rapidly during the first days of life with immediate signs of kernicterus, any level approaching 18 should lead to careful observation of the patient and preparation for exchange transfusion. Although it possesses its own case fatality risk, exchange transfusion is still the treatment of choice and should be performed one or more times as required to reduce serum bilirubin promptly to safe levels. Simple transfusion can add to the hazard by increasing bilirubin levels. Early signs of kernicterus can be reversible, the brain damage appearing to be a product of the bilirubin concentration and length of brain exposure to this concentration.

Since hyperbilirubinemia tends to be more common in the premature infant, it is often difficult to rule out the significance of a number of other factors in a resultant mental deficiency. The premature has a greater risk of having cerebral agenesis, birth injury, anoxia and prenatal infections. He is more apt to have received injections of vitamin K, which some believe can itself contribute to higher serum bilirubin levels, although in one carefully studied series the administration of vitamin K appeared to have had only a minor effect (34). Nevertheless, the liver of the premature is known to be deficient in its ability to detoxify bilirubin and it is probable that this mechanism alone can lead to the brain damage responsible for mental disease. Some suggest that the administration of glucuronic acid may aid in the conjugation and detoxification process and reduce serum bilirubin levels, but this procedure is still experimental and not without danger. Finally it should be noted that the antibody coated red cells of an erythroblastotic child are grossly deficient in oxygen carrying capacity and the resultant anoxemia may itself be a possible contributory cause of the brain damage (1).

A longitudinal study of the effects of a wide range of serum bilirubin levels is now being undertaken by Day and associates. Early findings suggest some measurable effect on growth and

development of the infant exposed to concentrations of bilirubin below the level of kernicterus toxicity (20).

Anoxia, Anoxemia, Ischemia

The newborn possesses both the greatest exposure to the hazard of asphyxia and the greatest resistance to its effects. Anoxia can cause the death of the infant but it is not known whether the survivors have a degree of brain damage sufficient to affect mental function. Darke (9) noted a 12 point lower than normal average I.Q. among children age 2 to 11 who suffered severe asphyxia at birth. Keith and Norval, on the other hand (22), found that survival meant no significant brain damage at least during the first few years of life, during which period they performed their observations. There is obviously a need for more extensive and prolonged longitudinal studies to supply definitive answers to this question. While the general lowering of the metabolism during periods of anoxia may protect the infant from the effects of inadequate oxygen, these secondary changes may in themselves be related to brain damage. From animal experimentation as well as some human studies, one must accept for the present that anoxia is a possible contributing cause of mental disease, although it can not be shown to be a major cause.

The epidemiology of anoxia and anoxemia is itself worthy of more intensive study. Birth injury, drugs given the mother for sedation, analgesia and anesthesia, prenatal hypoxia with contributory effects of the oxytocic drugs, infant infection, and congenital anomalies can each play a role. The exact importance of each is not well defined.

Brown (7) points out that while the infant is quite resistant to the CNS effects of anoxemia he is no better able to withstand ischemia than the adult. He believes that much of the cerebral pathology blamed on anoxemia is in reality due to the persistence of inadequate circulatory pathways after birth. Cardiac shunts, deficiencies in pulmonary circulation, neonatal shock, subnormal concentrations of pressor amines, may all lead to a

lowered cerebral blood supply. Hyaline membrane, a cause of anoxemia once believed due to the aspiration of amniotic fluid, now appears to be more closely related to improper circulatory mechanics, maternal diabetes, and disturbances of body water concentration. As Brown has stated, whatever its primary cause, recovery from hyaline membrane disease depends upon normal pulmonary flow, systemic pressure and cardiac output.

Anoxia and asphyxia in the adult are caused by nitrous oxide, drowning, carbon monoxide, or mechanical suffocation and can result in permanent brain damage in those who recover. Fletcher (12) has noted eight examples of permanent personality degeneration following nitrous oxide anesthesia. Similarly, after an unsuccessful attempt to commit suicide by hanging, the patient will suffer choreo-athetotic hyperkenesis, epileptic fits, and dysmnesia. Severe shock in the aged—such as that following hemorrhage, cardiac infarction, and surgery —can also lead to permanent brain damage and extreme dementia (3).

Carbon monoxide can be considered as a cause of anoxia because of its effect in reducing blood oxygen through the formation of carboxyhemoglobin. The characteristic chronic brain damage lesion is the destruction of the globus pallidus. Outside of suicidal attempts, carbon monoxide poisoning commonly occurs from exposure in automobiles or household heating, cooking, and refrigeration appliances.

After it had been established that exposure of the premature infant to oxygen concentrations over 40 per cent resulted in retrolental fibroplasia, some investigators noted that the blindness was accompanied by a higher incidence of mental retardation. Others found no such relationship and suggested that it was the association of retrolental fibroplasia and prematurity on one hand and prematurity and brain damage on the other which gave rise to the apparent association. In addition, there was the added environmental factor that blindness *per se* might be thought to reduce I.Q. because of its limiting effect on the learning experience. Parmalee, *et al.* (36) in a study limited

to blind school children between the ages of 5 and 9, were unable to demonstrate any difference in I.Q. between those blind as a result of retrolental fibroplasia and those blind from other causes. However they found a greater amount of mental retardation and neurological disorder in both groups than among sighted children. Another study by Norris (35) states that the children blinded by other causes have more mental retardation because of the high association of these conditions with neurological defects while retrolental fibroplasia produces the eye lesion as its only significant pathology. One must conclude that the weight of available evidence fails to incriminate excess oxygen as a cause of mental illness although the possibility has not been ruled out.

Trauma

Although persons with traumatic psychosis constitute only 1½ to 7 cases per 1,000 institutionalized patients (30, 6), there has been an increasing number of first admissions with this psychosis (27). Cases of traumatic psychosis in adults appear to be related to alcoholism, arteriosclerosis, and temperamental abnormality, but it is not known whether these conditions are caused by the trauma or constitute an underlying psychopathology which is exacerbated by it. Children have a 25 per cent better chance of surviving an equal amount of skull injury but no adequate follow-up has been made of the comparative mental effects.

A special study of penetrating brain injury showed that lesions of the frontal and occipital lobes did not produce a significant decrease in intelligence (46). However, lesions of the parietal and temporal lobes of the left hemisphere did result in marked deterioration in I.Q.

The more familiar pattern of brain injury following concussion can lead to a systematic disintegration of the mentality. The exact pathogenesis of the damage in non-fatal head injuries is not known, the most likely theories are the production of sudden cerebral anemia and the imparting of shear strains

to the brain (32a). Irreversible deterioration of personality and intellect and dementia are rare but dysmnesia, impaired concentration, and lessened spontaneity of thought are common. The particular form of brain damage from repeated concussion known as punch-drunkenness in boxers is characterized by many small brain lesions leading to a deterioration of memory and intelligence.

Poisons

Lead affects the nervous system as part of the cumulative end result of exposure over a long period of time with absorption occurring from either the alimentary or respiratory tract. Peripheral neuritis is a far more common symptom of lead poisoning than encephalopathy, but when it occurs it is associated with delirium and coma (32b). Children appear to be unusually susceptible and the resultant convulsions can leave permanent sequelae. Most of the other metallic and organic poisons produce an acute effect with neurological symptoms rather than a permanent psychoses or mental deterioration.

Alcoholism

Present estimates indicate that there are about five million alcoholics in the United States with a ratio of about 7 men to one woman (32c). Possibly one million of these have reached the stage where psychologic consequences have occurred. Malzberg (28) found that during Prohibition the percentage of alcoholic psychoses among admissions to New York State mental hospitals first decreased sharply and then increased after repeal to a figure of 10 per cent. Other more rural areas of the country show much lower percentages. Alcoholic psychoses are relatively higher in Negroes, rarer in Hebrews, and occur principally in middle age (14).

The more serious mental diseases appear to be more closely related to the consumption of spirits rather than to beer and wines. It is difficult to separate the effects of the brain damage from that of the intoxication. Heavy drinking for many years

results usually in a deteriorated personality, loss of memory, and even hallucinations. Some believe that most of the brain damage is not caused primarily by the alcohol itself but largely by the dietary deficiencies common in alcoholics.

The epidemiology of alcoholism itself is beyond the scope of this report. Suffice it to say that the search for personality types and environmental situations which predispose to alcoholism is being pursued actively. Although much has been learned, there is still great confusion and conflicting data. It is known that alcoholism can be preceded by a psychosis, a factor which makes it even more difficult to understand the significance of its association with mental disease.

Drugs

Barbiturates, cannabis, cocaine, and morphine are well known for their association with mental illness but there is no good evidence that their use is related to the development of any significant form of brain damage (32d). The habit is more prevalent among those who have psychopathic tendencies and the psychopathology of the acute and subacute states can lead to a progressive deterioration with poor prognosis but without clear cut evidence of brain lesion caused by the drug.

Infections

Bacterial meningitis can be caused by the meningococcus, pneumococcus, streptococcus, H. influenzae, M. tuberculosis, staphylococcus, and other organisms (51). H. influenzae is the most frequent agent associated with the disease in children except during periods of epidemics of other types. Meningitis in the pre-chemotherapy era was frequently followed by hydrocephalus, deafness, deafmutism, various forms of paralysis, epilepsy, and mental deficiency. In one series of 189 recorded meningitis cases, 12 per cent showed persistent cerebral damage and the majority of these had major mental retardation (2). Prevention of these conditions depends primarily upon prompt recognition of the bacterial meningitis with immediate treat-

ment with antibiotics before the lesions are extensive enough to result in permanent scarring.

Encephalitis is a term loosely used to describe a number of disorders which are associated with an inflammation of the brain. The exact etiology may be a virus which has a predilection for the CNS, or it may be an allergic or degenerative condition.

The epidemic encephalitides due to arthropod borne viruses which invade brain cells can result in severe brain damage and mental impairment. Equine encephalomyelitis is particularly damaging to infants with 54 per cent of its major sequelae occurring in those in the first year of life. St. Louis encephalitis has an incidence of major sequelae between 1 per cent and 8 per cent. Although these diseases are relatively rare, their occurrence is always alarming because of the great risk of the serious residual brain damage suffered by their victims (32e).

Mumps meningoencephalitis is the commonest example of a nonarthropod borne virus which invades brain tissue. It can occur in the absence of parotitis (15), but usually accompanies the classical syndrome. Army studies suggest that when a routine spinal tap is done, over half of the cases are found to have signs of virus invasion of the CNS, as compared with one-third who have clinical disease of the nervous system. Other studies dealing with other age groups indicate a far lower risk of meningoencephalitis in mumps. The basic lesion on necropsy studies is a perivascular demyelinization more closely associated with the post-infection encephalitis than with direct virus infection of the brain.

Mumps meningoencephalitis has a curious sex predilection with about seven times as many cases occurring among males as in females (24). Sequelae are rare, usually two or three per cent and then usually of minor nature although serious after effects have been noted. The great frequency of mumps, the fact that mumps occurs most usually in children who appear more susceptible to brain damage, the possibility that this encephalitis can occur during an episode of inapparent mumps

infection, the frequency of the CNS response during mumps, all give the disease added significance in a consideration of the relationship of brain damage and mental disease.

Other viruses which invade CNS tissue include the ECHO viruses, Coxsackie viruses, and others associated with the term "aseptic meningitis" (31). The epidemiology of many of these viruses is quite complex with a variety of animal hosts capable of playing a role in the ecology of the virus. Moreover, one cannot be certain that a given virus strain has a true cytopathogenic effect or that the isolation of a given virus from a case of encephalitis means that a true culprit has been found. It appears probable that many of these viruses can cause encephalitis and that residual brain damage does result from such infections. Further exploration of this field requires expanded use of tissue culture and probably the development of even newer techniques.

Measles is accompanied in about one case per 1,000 with a post-infectious encephalitis (31). The lesion is believed to be a "defense" mechanism of the CNS rather than a tissue invasion by the virus. Experimental studies have indicated a similar pathologic demyelinization response as an allergic reaction to tissue extracts. It has been presumed that the inflammatory reaction is the result of a tissue immunity and the plasma cell has been suggested as the site of action between the antigen and the neurone. If it is true that post-infection encephalitis is an allergic manifestation then the still unsuccessful search for a means of detecting the allergic predisposition and its therapy are of the greatest importance. Sodium salicylate and P. aminobenzoic acid are said to have some therapeutic effect. At the present time the best method of preventing this complication of measles appears to be the administration of gamma globulin.

Post-infectious encephalitis also follows smallpox vaccination (vaccinia), and immunization with some killed agents such as rabies vaccine and pertussis (31). The rabies vaccine effect is apparently associated with an allergic reaction to the contaminating extract of animal brain. Use of the new duck em-

bryo vaccine instead of the Semple material is now expected to remove this risk. The triad of fever, convulsions, and irreversible central nervous system changes following pertussis vaccine administration resembles that seen in some severe cases of pertussis. Although the symptoms have also been noted following the inoculation with diphtheria toxoid, typhoid, and influenza vaccine, pertussis vaccine appears to offer the greatest risk especially when given in the rapidly absorbed saline solution (16, 40, 4). Most of the children affected gave a history of central nervous system instability, and males appear to be affected twice as often as females. Children with a history of convulsions should be immunized only with monthly fractional doses and premature, frail, or ill infants should have the immunization postponed. It is not known whether the effect is due to a sensitization, a toxin of the organism, or primarily due to a constitutional susceptibility of the host. Although only a little over 100 cases have been reported in the literature, the persisting physical and mental morbidity rate of 30 per cent and the case fatality ratio of 15 per cent indicate that when it occurs this is a grave complication of a routine procedure.

Syphilis

Hahn, *et al.* (18), state that as the incidence of syphilis itself decreases, dementia paralytica is becoming something of a neuropsychiatric rarity. Approximately 5 per cent to 10 per cent of inadequately treated syphilitics will progress to late neurosyphilis. Between 1920 and 1950 the number of paretics admitted to New York State mental institutions dropped from 13 per cent of admissions to 2 per cent. The disease was uniformly fatal prior to von Jauregg's discovery of malaria therapy in 1917 but now is curable in some and partially remedial in many due to the advent of penicillin. Deaths from paresis in Great Britain between 1916 and 1955 dropped from 2,100 to about 200. In his series of 1,086 paretics, Hahn noted 60 per cent were simple dementing, 18 per cent manic, 6 per cent paranoid, 3 per cent with somatic signs only, and 7 per cent un-

classified. Even with specific penicillin therapy the death rate for paretics was still four times that of a comparably aged non-syphilitic group, a selective mortality which tends still further to decrease the prevalence of paretics. The best treatment is prompt detection with early and adequate treatment of syphilis in its early, pre-nervous system stage, and present syphilis control programs are undoubtedly responsible for most of the rapid fall of paresis. Congenital syphilis is also now exceedingly rare, and there has been no increase to parallel the recent rise in early syphilis. In one British series of 1,900 institutionalized mental defective children only 12 had a history of syphilis (5). The authors conclude that mental deficiency due to congenital syphilis will disappear.

Degenerative Encephalitis

The commonest form of degenerative encephalitis is multiple sclerosis, but the group also includes acute diffuse encephalomyelitis, Schilder's disease and Balo's concentric sclerosis (31). These are demyelinization processes which can be differentiated by micropathological examination from the post-infectious encephalitides. The etiology of these conditions is unknown, with allergy and certain predisposing factors believed to be of possible significance.

A number of epidemiologic studies have pointed out interesting associations which suggest etiologic hypotheses. A series of 39 families were studied in which there were three or more cases of multiple sclerosis. Others have found geographical differences with a higher incidence in northern areas, such as a six-fold higher rate in Winnipeg compared with New Orleans. Sutherland (43) suggests an ethnic predisposition in the Nordic in contrast with greater resistance in the Celtic race. It must be recognized that none of these epidemiologic studies is conclusive because of difficulties in differentiated diagnosis, small numbers, and lack of pathologic control. Despite the fact that experimental injection of myelolytic substances, ergotamine, potassium syanate, and other toxic agents may each produce

lesions suggestive of multiple sclerosis, no such mechanism has been shown to play a role in the human disease. Swank (44) suggests that multiple sclerosis is due to a high fat intake and substantiates his statement by an association of disease incidence with areas of high fat intake in Norway. However, other possible factors have not been ruled out nor has the theory yet received definite corroboration from studies of the response to adjustment of the diet of multiple sclerosis patients.

The incidence of intracranial tumors in childhood rises to a maximum at 5 to 8 years of age, falls, and then rises to a secondary peak at ages 10 to 12. Brain tumor incidence reaches another peak during the middle years of life. They usually develop slowly, giving the classical signs of intracranial pressure which may be delayed in the infant. Convulsions, difficult gait, and behavioral changes, such as lack of interest in school work, can be noted. Seventy per cent of patients with cerebral tumor are said to show some psychological disturbances, many of them in the early stages of the lesion. Recent surveys indicate an incidence of cerebral tumor of 4.6 per cent among inmates of mental institutions (23).

The glioma is the most common pathologic form, responsible for about one-half of all cases, with the spongioblastoma multiforme variety of glioma causing about one-quarter of the total cases. Meningiomas also appear in one-quarter of the patients afflicted with brain tumors. The remainder is made up of tuberculomas, gummas, metastatic, pituitary, acoustic, hypophyseal duct, and blood vessel tumors. The metastatic tumors appear as the most frequent tumor of this last group.

Deficiency Diseases

Cretinism has been observed in some mountain areas of Europe to occur with endemic goitre. It has later been found in inland areas over a wide area of the world. In 1933, Penrose estimated the frequency of hypothyroidism among mental defectives in institutions at 3 to 5 per cent (32f). Sporadic cretinism due to the absence of a thyroid gland still occurs with the

same frequency, but cretinism of the endemic type related to deficient iodine intake has decreased with iodization of salt and improved food distribution.

Congenital hypothyroidism can be diagnosed by the age of 3 months and always before 6 months if the characteristic symptoms of lethargy, constipation, respiratory distress, frequent infection, dry skin, thick tongue, hoarseness, and umbilical hernia are noted (26). In some instances even early treatment will not give a good mental result and in such cases an independent primary mental defect has been suspected (49).

Pernicious anemia is associated with a subacute degeneration of the brain. The pathologic process is unique and is distinguishable from that due to pellagra and other diseases involving cerebral white matter. The resultant mental symptoms are not characteristic, taking the form of a severe mental disturbance with paranoia or delirium. The pathogenesis appears related to a decreased cerebral metabolism due to a vitamin B12 deficiency and not to the anemia (47). The condition can be reversed if treatment with the vitamin is begun early. If one withholds treatment after the cerebral symptoms occur, while attempting to make a hematologic diagnosis, brain damage can result. Most improvement will occur during the first 3 to 6 months of therapy, and relapses associated with infections can be corrected by increasing the dosage of vitamin B12.

Diarrhea, anoxemia, or excessive salt ingestions may lead to hypernatremic dehydration (11). This condition can also arise from a central nervous system injury which alters the regulatory mechanisms for homeostasis of water and electrolytes. Hypernatremia in turn may result in subdural hematoma and brain injury. The hypernatremic condition is reversible if treatment to restore the proper electrolytic balance is begun before permanent brain damage occurs.

The earliest descriptions of pellagra made mention of the presence of mental symptoms, and pathologic studies have confirmed the presence of marked changes in the Betz cells of the motor cortex, the frontal lobes and the periventricular

areas (32g). Pellagra arises from a multiple deficiency of vitamins of the B group, including thiamin and riboflavin, but especially of nicotinic acid. Chronic alcoholics, because of their poor diets, appear to be especially susceptible to pellagra which appears characteristically in any low economic population on a cereal diet. The disease becomes worse in the spring, probably because it follows a winter diet deficient in fresh vegetables.

Treatment by nicotinic acid usually results in improvement of the psychiatric symptoms if the brain damage has not progressed too far. Therapy with additional components of the B vitamin group must be approached cautiously because it may upset the vitamin balance and lead to an exacerbation. Pellagra psychosis is decreasing dramatically in incidence in this country with the general improvement in diet.

Wernicke's encephalopathy (32h) appears to be likewise associated with vitamin B deficiency, perhaps primarily a thiamin deficiency. Hence it can be looked upon as a severe form of beri-beri. Congestion and hemorrhages in the gray matter of the brain-stem and mammillary bodies of the hypothalamic region appear as the chief pathologic findings. The disease occurs with severe alcoholism or malnutrition and appears to be an acute response to a low level of thiamin in the body, superimposed upon a background of nutritional deficiency. Since the disease is a late manifestation of a long standing nutritional disorder, therapy with thiamin usually does little to reverse the mental disturbances.

A recent British study suggests an association between intelligence and nutritional adequacy among school children (21). Seventy-three per cent of children in schools for the educationally subnormal were below average in weight and 68 per cent were below average in height. This is a poorly controlled study, and it is obvious that such a finding can only be useful in suggesting new paths for epidemiologic exploration. It is mentioned here to fill a gap in the discussion of nutritional deficiency. Although severe deficiency can result in mental disease, such situations are becoming increasingly rare. Modern effort

must seek to explore the effect of lesser degrees of sub-optimal diet. Mental hospitals report that patients admitted in a poor nutritional state improve with dietary supplements (17).

Convulsive Disorders

Epilepsy, the most common of neurological disorders, affects 1,500,000 Americans. The low threshold of the neurones subject the brain to frequent mass discharges, which take such forms as attacks of grand mal or petit mal. In the psychomotor form of the disease the temporal and frontal lobes are affected, leading to "automatisms." As is true in all forms of epilepsy, the patient has amnesia for his psychomotor attack.

Seizures may be related to a number of factors which damage neurones, such as head injuries, congenital defects, birth injuries, brain infections, brain tumors, fever, and defects in cerebral circulation. Such lesions can produce a small area of scarring in the brain which serves as the source or focus for the start of an epileptic attack. In most cases the etiology is unknown, and hence 70 per cent of cases are termed idiopathic.

Hereditary factors are traditionally believed to play a role since if one of a pair of identical twins without known prior brain damage was epileptic the other was also epileptic in a majority of instances (19). Even among those whose epilepsy follows a brain injury, a family history of epilepsy is three times as common as among the general population. For idiopathic epilepsy the incidence is said to be seven times as great in the near relatives of the patient. However, other factors could account for this apparent genetic relationship, such, for example, as the greater frequency of prematurity among twins, which, itself, is related to greater risk of brain damage.

Studies of the prenatal and perinatal period indicate the existence of more abnormalities for epileptic children than for matched controls (25, 37). It is possible that amino acid metabolism plays a role in epilepsy but the experimental findings have not yet demonstrated the mechanism of action. The search for some chemical explanation of neurone hypersensi-

tivity is being pursued actively and is the most attractive hypothesis which could explain both the seizures and their response to the anti-convulsant drugs.

An epileptic attack following a high fever from a non-specific infection is most common in the child under age 3. Therapy to reduce the fever is indicated, since a certain proportion of cases develop the idiopathic form of epilepsy at a later date, especially if the first febrile convulsion occurred in infancy. In addition, a tendency toward repeated febrile convulsions is the rule and may lead to brain damage. Hence continuous anti-convulsant drug therapy up to age 3 or 5 is recommended by many after even one such attack; by all after two or three. The younger the child at the onset of convulsions, the more likely he is to become mentally retarded (23). In later life mental deterioration is more apt to occur among those epileptics whose disease is associated with injury to the nervous system than those with idiopathic epilepsy. Mental impairment is most commonly seen in the psychomotor syndrome, next in grand mal and is least likely with petit mal.

Convulsions from any cause, if severe, repeated or prolonged, can lead to anoxia of the brain with damage to the neurones. The goal of therapy must, therefore, be aimed at reducing the number and duration of the seizures. Caution should be used in withdrawing drugs completely even after years of freedom from symptoms, since there is a 50 per cent chance of recurrence. Even with adequate drug therapy, 75 to 80 per cent control of seizures is the best that can be expected. Despite the association of mental deterioration and epilepsy, 67 per cent of epileptics are found to be of average or superior intelligence, 23 per cent slightly below normal and only 10 per cent grossly deficient (50).

Cerebrovascular Disease

During the past decades there has been a striking increase in the incidence of psychosis associated with cerebral arteriosclerosis. In New York State mental institutions, the propor-

tion due to this condition rose from 7.8 per cent in 1920 to 14.3 per cent in 1930 and 19.9 per cent in 1940 (29). These relationships are not appreciably changed after they have been standardized for age: 21.3 per 100,000 population in 1920, 44.4 in 1930, and 66.7 in 1940. The arterial disease decreases the blood supply to the brain with resultant neurone necrosis and increases the risk of infarcts and brain hemorrhage which cause even more extensive brain damage.

The epidemiology of cerebrovascular disease has been studied but the findings are not very revealing. One of the most extensive investigations has been reported by Takahashi and coworkers (45) in Japan. This particular country has a low mortality from coronary heart disease—the chief cause of mortality of Occidental countries—and cerebrovascular disease is now its leading cause of death. Takahashi found the incidence highest in the northeastern areas of the country except for Hokkaido. The distribution of average blood pressure, hypertension and hypotension seem to parallel the death rate from cerebral hemorrhages, if one accepts the general belief that hypertension is a predisposing disease. The authors conclude that low outdoor and indoor temperatures are responsible for the vascular phenomena. They also note that areas of high incidence are those whose inhabitants eat more rice and salt and less vegetables. These studies are also poorly controlled and the findings are of importance merely because they suggest further explorations.

Ecker (10) studied 20 patients with cerebrovascular disorders and found that 13 had a history of longstanding personality disorders preceding a stroke, in 15 special emotional stress immediately preceded the stroke, and in 8 cases both factors were present.

Vasospasm of the larger cerebral arteries can lead to cerebral edema and permanent neurologic disease (38). It is now believed that most first serious episodes of stroke are preceded by one or more "little strokes" which may be vasospasms, small thrombi, emboli, or cerebral insufficiency associated with nar-

rowing of the arteries of the brain (42, 8). The administration of anti-coagulants may decrease the incidence of thrombosis. However, their use also brings the danger of hemorrhage and may lead directly to further brain pathology. Nevertheless, anti-coagulant therapy appears to exert a favorable influence on the future of patients who have suffered their first stroke (48).

An interesting review of hospital first admission rates for senile psychosis has been performed in Onondaga County, New York (33). Significant differences were found in the sex specific rates between urban Syracuse (with the highest rates) and the more rural remainder of the County. Even in the latter the villages had higher rates than their truly rural surroundings. The village with the lowest admission rate was the one with the highest concentration of foreign-born—white persons of Italian, German, and Polish extraction—a finding which was also noted in the analysis of the data for urban Syracuse. The authors note that these findings could be caused as well by an in-migration of the mentally ill into the high prevalence areas or a higher tendency toward hospitalization from these areas, as by a true etiologic relationship based upon environmental or ethnic differences between these areas. Their own studies do indicate that admission rates tend to be higher for populations which live within twenty miles of a mental hospital. This effect appears to be diminishing, and it may be a chance association with other variables which are significantly related to the prevalence of senile psychosis.

The current state of knowledge of the mechanisms possibly related to the occurrence of cerebrovascular disease have been reviewed by Scheinberg (41). An extensive account of these is beyond the scope of this report, and present knowledge is too inadequate to give definitive answers. Similarly, a discussion of the epidemiology of the two major forerunners of cerebrovascular disease, hypertension and arteriosclerosis, is too complex to be included here. It is worth noting that arteriosclerosis of the coronary arteries has a different geographic and ethnic

distribution from that of the arteries of the brain. The confusion which exists in reaching an exact clinical diagnosis of both of these conditions further complicates the problem for those performing epidemiologic studies in this realm.

Conclusion

This review of the relationship of brain damage after birth and mental disease will be concluded with the same general impressions with which it was begun. Although many clinical and pathologic conditions associated with mental disease have been identified, the epidemiology of these underlying conditions requires much more exploration. Present data are sufficient to be useful in controlling much brain damage due to jaundice, anoxia, ischemia, poisons, alcoholism, bacterial and treponemal infections, some varieties of deficiency diseases and epilepsy. They are inadequate to offer much against the virus diseases, trauma, degenerative conditions, most tumors, and cerebrovascular disease. It must be admitted that the greatest number of patients suffer from mental disease associated with brain damage which is still not preventable. The hope for an understanding of these mechanisms sufficient to permit ultimate control lies in future research. Epidemiologic studies should comprise a major portion of this research effort.

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DR. JAMES: I have one comment to make, namely, that this particular field, as I am sure everyone knows, has an extremely voluminous literature, and the very size of it made me more terse than perhaps I should have been.

Let me just set myself up for real criticism by saying that the selection of the papers to be noted was done by me on purpose, so that if the selection is a poor one, I am to blame.

There are a large number of references that could have been mentioned that were purposely omitted merely to keep it in some manageable proportions, and in re-reading it several weeks after the event, I was a little surprised at its terseness and with the fact that I had selected very few references in many controversial areas.

DISCUSSION

DR. BENJAMIN PASAMANICK: I find myself in the same position that the other discussants did, that is, not knowing the field under discussion very well. Therefore my comments will have to center on Dr. James' paper rather than adding much to what he has written.

In the first place, I found this particular area in a rather interesting state. There is much greater variation in the state of knowledge and investigation in this area in contrast to the social, psychological, and cultural areas, both as to the variables involved and as to the hypotheses to be considered.

For instance, let me point out that in such conditions as measles encephalitis, measles is a necessary condition by definition but I think we can state that when we find retardation immediately following upon measles encephalitis there is very little doubt about the causative relationship.

However, when we come to the predisposing and precipitating factors for encephalitis and brain damage we have very little knowledge in this field, and really poorly defined hypotheses for epidemiologic investigation.

This is true of many of the factors discussed in this particular review. After reading Dr. James' paper and reading some of the references he cited, I was surprised by this finding and somewhat consoled for our own deficiencies to discover that so many of the studies were poorly defined, lacked controls, and definitiveness. Much needs doing and redoing epidemiologically.

I have a few comments which refer to specific points in the paper. I agree with Dr. James that the role of hyperbilirubinemia is still not well understood. I think that we ought to recommend more routine maternal and paternal incompatibility studies because, by determining the presence of incompatibility and antibodies in the mother, we have the capacity to predict when jaundice is likely to occur and prepare for exchange transfusions.

An interesting finding that I have gleaned from some of the pediatricians is that ABO incompatibility seems to be decreasing or almost disappearing with the cessation of the administration of Vitamin K and this then brings up the whole matter of iatrogenic conditions.

Gantricin administration, for instance, in newborns also seems to be implicated in this whole sensitivity area.

I think as we get more and more specific therapeutic agents and do more and more to patients, we have to think more often of the possibility of doing damage. There seems to be competition in the enzyme systems of the premature and the newborn in response to the administration of some of these substances. I think that there seems very little question at this time that Vitamin K is damaging.

Day, in a further remark on the administration of glucuronic acid, indicates that glucuronic acid administration simply doesn't work.[1]

[1] P. 85.

Following this, is a discussion of anoxia, anoxemia and ischemia.[2] Dr. James makes reference to Darke's work. In that regard I would like to point out that Darke eliminated cases with positive neurological findings. Those are just the kinds of cases which would have had intellectual retardation. While Darke still found significant changes, Keith and Norval later did exactly the same thing in eliminating cases with positive neurological findings in a similar study of the sequelae of natal apnea, but they did not find any differences. They also reported, in a somewhat better controlled study, that they didn't find any effects of anoxemia at birth with later behavioral functioning in infants.

We, too, do not seem to find this when we eliminated the prior occurring complications of pregnancy and prematurity.

In Dr. James' discussion of blindness and retrolental fibroplasia and effects of blindness on development,[3] I think the evidence indicates that blindness in and of itself probably does not have much if any effect on intellectual potential. I think the reason so much defect is found in non-premature blind children is that most of these are due to congenital neurological defects, and when we have congenital defect, we usually have more than one in the central nervous system, and this probably accounts for the intellectual deficit. Clinically we seem to have a difference between defects distal to the retina, and those involving the retina, because the latter being a direct outgrowth of the central nervous system would probably accompany other congenital central nervous system defects. In our premature study, I don't think we found any difference in the amount of defect between those with, and those without, retrolental fibroplasia in infants under 1,500 grams, so that I don't think that oxygen administration to the newborn has much effect on the central nervous system.

When we come to physical trauma,[4] Dr. James remarks that there is an increasing number of first admissions of traumatic psychosis. How much of this is due to better diagnosis and also to saving more individuals from death? With regard to lead intake in children, we have surprisingly little proof that lead causes mental defect. The evidence, although seemingly good, is not really definitive.

I think we ought to spend a bit more time on such conditions as

[2] P. 86.
[3] P. 87.
[4] P. 88.

alcoholism and cerebrovascular diseases because these really contribute enormous numbers to the mental hospital population and to disability in general, in contrast to some of the other conditions mentioned in this particular paper.

Let me give you some indication of the complexity that exists in some of the variables under discussion. When we come to the remarks on infections as causing brain damage, matters are not quite as simple as they appear. For instance, we have found that in brain injured children we get a significantly higher rate of illness, both hospitalized and non-hospitalized, during the first year and probably afterwards. A good many of these illnesses are infectious in nature, so that this variable of brain injury must be factored out even in a discussion of infection as a post-natal factor. Is an already injured brain more susceptible to infection?

In addition to this, since we have relationships between socio-economic factors and infection and brain injury; and, in turn, intellectual functioning with socio-economic factors (all of which confound the effects), matters are not as simple as they might be, in epidemiologic studies, even in something as seemingly clear-cut as the relationship of infection to brain damage.

As to syphilis, I wonder what is going to happen as our vigilance decreases in case finding in syphilis? I have found that the pediatricians are beginning to forget about syphilis in differential diagnosis of conditions in children, and they have to be caught-up on this now and then because we still find congenital syphilis and even primary syphilis in children.

In the deficiency diseases, when we come to cretinism, we are beginning to suspect that the results of treatment with thyroid in cretinism are not related to time of administration of the medication. I think that we have found higher intelligence quotients in many early treated cases because these occur in children coming from higher socio-economic backgrounds, those that get medical care earlier. We continue to find a large number of defective children, even with quite early institution of thyroid treatment. On the other hand, there are a large number of children who seem to do quite well even when thyroid is administered later during infancy.

My remarks however ought to be confined wholly to infancy. If we start giving thyroid to three or five-year old children, I think we probably would be too late.

Dr. James remarks on an association between intelligence and nutritional adequacy among school children.[5] Again this is not as simple as it appears. A quite possible explanation is that the children who are physically subnormal because of socio-economic status, are also mentally subnormal because of the same reason, and nutritional deficiency is merely associated with both. However, the situation is probably confounded in that all three variables are involved.

Dr. James speaks of hereditary factors as undoubtedly playing a role in epilepsy because of the findings in twin studies.[6] I am not so certain about the hereditary factors on the basis of this evidence. For instance, we have known for a long time that identical twins are more subject to brain damage than non-identical twins so that a higher rate of concordance would be expected for monozygous and dizygous twin pairs. The evidence also seems to indicate that twins have a much higher rate of epilepsy than do singletons in the population. I would like to point out that family histories of a disease are notoriously biased in the direction of the disease under scrutiny since histories of the disease in cases and controls are not secured under comparable circumstances, and that the family history evidence of epilepsy is therefore not a very good one.

I have just one final comment on cerebral vascular diseases. As to the striking increase in the incidence of psychosis associated with cerebral arteriosclerosis, I think we all recognize that this may largely be due to failure to die from some other cause, such as infection, and also to lack of chronic disease facilities. The inadequacy of facilities for care of the aging causes admission to mental hospitals as one of the few places you can put chronically ill individuals.

This brings up the whole matter of reversible damage, which has largely been omitted from Dr. James' review. I wonder how many patients labeled as psychosis with cerebral arteriosclerosis, or senile psychosis, are admitted to mental hospitals because they had one or more chronic disorders such as heart disease? Being bedridden for lack of adequate care, they became confused as a consequence of some minor anoxemia, and were quickly shoved into mental hospitals because they could be taken off local budgets and put onto state budgets, where they remained confused and psychotic because of inadequate care.

[5] P. 97.
[6] P. 98.

I think this is merely an indication of the need for more discussion of the two conditions that I mentioned—alcoholism and cerebral vascular disease.

SUMMARY OF THE GENERAL DISCUSSION

1. In his paper, Dr. James considered that hereditary factors undoubtedly played a role in epilepsy. There was disagreement on this point. Epilepsy is no longer thought of as a disease and, therefore, there is no reason to expect results from genetic investigations. Many of the ideas about epilepsy, which are still circulating, are based on old studies of twins in Germany by Kornwall. He worked with institutionalized epileptics who in most cases were also mentally deficient so that the data were heavily biased, being really studies of mental deficiency with seizures as accompanying symptoms. In Sweden, a committee of various specialists is presently engaged in revising a 17th century law that prohibited so-called idiopathic epileptics from marrying, since evidence, in part based on studies by Bjornstrom, indicated that there is no reason to maintain the law.

It was doubted whether such a thing as idiopathic epilepsy existed in the sense that seizures arose "spontaneously"; this suggested a genetic etiology in the absence of other apparent causes. From the studies done in Sweden it appeared that such seizures could be traced in the histories of the patients to a variety of causes, such as alcohol or infection.

Finally, it was noted that there is no good evidence, either, for a genetic factor that predisposed to seizures in conjunction with any specific cause. For example, in cases of battle injuries to the head only a small percentage of cases developed traumatic epilepsy. But if such cases of a specific known etiology were compared with cases of unknown etiology it was found that there was the same incidence among the siblings of both groups, about 2.5 or 3 per cent.

In the case of cretinism, on the other hand, some recent studies seem to indicate a genetic factor, especially where there was inbreeding as, for example, in the valleys of Switzerland and Austria. The disease then is not entirely a matter of thyroid deficiency and iodine insufficiency, but is apparently complicated in some cases by a recessive genetic factor.

2. Meningococcus meningitis needs to be mentioned with syphilis as a disease that could very readily be overlooked because it has generally been so well controlled. Recent experience in Maryland showed an increase in deaths from the disease, and it is therefore highly likely, though not demonstrated, that there is a parallel increase in the number of persons suffering brain damage from the disease, such as mental deficiency or deafness. The disease must still be considered dangerous and a high index of suspicion for it should be maintained in diagnostic work-ups.

3. The relationship of blindness to mental retardation was discussed. Since in our society, a blind individual tends to be marginal in a number of ways, might not this social factor affect the individual from infancy, contributing to whatever mental retardation that occurs?

4. It was suggested that brain damage possibly has a bearing on symptoms labeled as psychoneurotic. While this is a difficult area, it is an important one. Apart from the longitudinal studies presently being done abroad which offer some bare suggestive evidence of such a relationship, there exists no evidence to this effect, a fact that has been interpreted in support of the purely psychological explanation of psychoneurosis. But is this lack of evidence due to none having been found or because not enough effort has been expended?

5. Some pointers for research in this field of damage to the brain were made. While it is believed that early detection leading to prompt treatment is the key controlling many conditions, it was noted that in some the evidence for this belief might be spurious. This was suggested by McKinney in Canada, when he proposed that the decisive factor in breast cancer is the speed of progress of the disease. While it might seem that the time of making the diagnosis affects the prognosis, actually it is the progressiveness of the disease that affects both of these other variables. Thus the more rapidly growing-type of cancer tended both to be seen late and to have a poor prognosis. The same situation might occur in cretinism. If so, the time of administration of thyroid was a relevant question.

6. Another point relevant to a better understanding of cretinism was illustrated in the relationship between sickle cell anemia and malaria, where the same factor that is responsible for vulnerability to the anemia also gives protection against malaria. Thus it might be worth inquiring as to whether there is some biologic "good" asso-

ciated with cretinism which acted as a defense mechanism against another harmful contingency.

7. The enormous French literature on alcohol and psychosis, which uses a somewhat different approach from that of the Anglo-Saxon world, remains completely ignored in both the United States and Britain. Much the same could be said of the very extensive Japanese genetic literature on twin studies. While there were some barriers in communication or comprehension, there seemed to be no effort made to overcome them. This is a defect in outlook and mode of work, since attention which is confined merely to what is congenial is evidence of cultural bias on the part of investigators.

Some impressions of the French studies, based on fragmentary acquaintance of the literature, was offered. A number of studies compared admission rates for alcoholic disorders by geographic areas and by subsections of the population, finding striking differences between, for example, various groups of immigrant laborers and native Parisian laborers; between wine-growing and other districts, or in relation to toxic factors affecting the wine harvest from one year to the next.

8. Other specific substances related to brain damage not discussed by Dr. James in his paper, included benzedrine, whose effects in addicts were seen in admixture with the psychopathic traits that made persons prone to addiction. Benzedrine psychosis was increasingly being taken into account in Britain, while Japan's considerable benzedrine problem stemmed from the forced use of the drug during the war as a means of increasing production. Benzedrine has also been implicated in acute psychotic episodes in non-addictive cases, where attacks were diagnosed as acute schizophrenia, and this experience shows the importance of looking for benzedrine as a possible organic factor.

Prominent amongst the other drugs in common use that should be considered with suspicion are the bromides and tranquilizers.

Some evidence was found in Britain that prolonged anesthesia in elderly patients accelerated mental deterioration. However, very little work has apparently been done on the matter.

9. Among deficiency diseases, protein deficiency raised challenging questions. The mental effects of kwashiorkor during the acute stage were striking; and there was the impression that severe cases produced lifelong sequelae. This suggested that in areas where

"kwashiorkor" as such had not been reported (perhaps in the South or the Southwest of the United States) similar protein deficiencies might be going by some other name.

10. Alcohol, apart from its direct role, needs to be considered because of its enormous influence in traumatic brain damage. Figures that indicated the extent of the problem were alarmingly high. It has been said that as many as 80 per cent of fatal automobile accidents involve drunkenness, while 25 per cent of all admissions to Bellevue Hospital directly involved alcohol. In associations of multiple factors in etiology, alcohol holds a most prominent place.

DR. JAMES: One of the points of reference for this paper was the occurrence of brain damage. Although the drugs which have been mentioned by several of the discussants can cause acute conditions (Point 8), I was unable to find clinical evidence of their relationship to the development of detectable organic brain damage.

The fact that this report did not include a more extensive discussion of the major conditions is a real criticism, and I was well aware of this while writing the paper. The conditions with the best known epidemiology appear to be those with the lowest incidence and prevalence: jaundice and encephalitides for example. Although the major problems, like alcoholism and cerebrovascular accidents, are the subjects of a voluminous epidemiologic literature, this literature is confusing and offers very few lines of clear evidence. Even the best of it seems only to suggest a few hypotheses whose value rests mainly upon the fact that they suggest where additional studies should be performed.

The Takahashi paper (45) intrigued me because it did present a definite hypothesis. However, the usual bias due to the inadequate diagnosis, pathologic controls and follow-up makes it impossible to accept this hypothesis as anything other than an interesting problem for further study. I included it because, as a generic paper in this field, it illustrates the difficulties one encounters in performing epidemiologic studies, the weaknesses of the final conclusions, and the huge task it will be to pursue these leads by an adequate epidemiologic investigation.

In general, every one of the underlying conditions discussed in this paper is itself a subject for extensive epidemiologic study, and these pathologic complexes are related to much more than brain damage

and mental disease. A discussion of cerebrovascular disease will lead into a review of the differences in the epidemiology of atherosclerosis when it occurs in the coronary arteries, the cerebral arteries, or aorta. It would have been an enormous task to have included a useful review of this subject and, as was pointed out, it was considered beyond the scope of the present discussion.

I think the comments on cretinism (Point 1) illustrate a problem in epidemiologic reasoning which has been noted in some of the earlier discussions today. When a cretin did not improve after the administration of thyroid, he was given a different diagnostic label. It was said that his cretinism was due to a condition that would not respond to thyroid. Although this is circular reasoning, it can be a significant first step in the classification of disease and help define different epidemiologic groupings for further exploration. At present it leads to confusion if one attempts to explain the proper role of thyroid function in patients now classified as cretins.

It was noted in the report on jaundice that the erythroblastotic child can get into difficulties because of several possible mechanisms. His red cells coated with antibody may not carry oxygen as well as normal red cells, leading to brain damage from anoxemia. On the other hand, the bilirubin itself can be directly toxic to the brain. It is difficult to be certain which factor is the cause of the brain damage. This illustrates another difficulty encountered in drawing conclusions from the existing reports in the literature.

Dr. Pasamanick in his opening remarks noted correctly that the British study on nutritional deficiency was designed poorly and does not permit one to draw etiologic conclusions. The investigation was included only to illustrate a general approach which, if properly performed, might be useful in a study of the epidemiology of these conditions.

Although many of the well-outlined conditions associated with mental disease occur rarely, it is possible that their more frequent sub-clinical stages might be related to mental diseases to a greater degree than we now suspect.

The exploration of the role of suboptimal amounts of nutrients or serum levels of bilirubin slightly above normal as possible agent factors in brain damage might be a fertile field. The studies of the New York group on the effect of slight elevations of concentrations of bilirubin in retarding development of the newborn are suggestive.

Our understanding of the epidemiology of brain damage due to the infectious agents, as some of the discussants have noted (Point 2) is far from complete. We do not know the basic mechanisms involved in pathogenesis; we do not know why one person develops brain lesions while another, with a more severe degree of infection, does not. Whether this is due to host factors, such as a genetic susceptibility or a temporary change in the physiologic state, is not known. It is true that most of these are rare conditions, but an elucidation of the basic mechanisms involved in the different host responses might do a good deal to improve our knowledge of the causes of brain damage.

As far as the diagnosis of syphilis is concerned, I am not aware of any clear evidence that a lowering of the index of suspicion has resulted in any greater incidence of brain damage (*see* Point 2). It is true that we are having more early syphilis, although still far less than we had two decades ago. However, we have yet to note any increase in late syphilis during these past few years, and its decline has continued to the point where symptomatic tertiary syphilis is fast becoming a clinical rarity.

I would like to close these remarks with a few comments about the field of organic brain damage and mental disease. Of all of the categories of mental illness, this might seem to be the one most easily grasped and most easily attacked. Our review has indicated that it suffers from the same problems of diagnosis, reliability, and validity which were noted in our discussions of each of the classifications of mental disease.

The need for cohort studies is obvious. The fact that very few good ones have been done is discouraging to today's reviewer but offers a challenge to tomorrow's investigator. It is doubtful that we can learn a great deal more by continuing to review in depth the many reports, largely based upon retrospective studies, which have supplied the mass of existing data in this field. Rather let us spend our efforts in fresh starts, possibly based upon some of the intriguing hypotheses which do evolve from a review of the past literature, and utilize statistical designs which will permit more assurance in our chains of inference.