PHYSICAL DAMAGE TO THE FETUS

BRIAN MacMAHON, M.D. AND JAMES M. SAWA, B.S.

INTRODUCTION

THE literature on prenatal influences in mental disease is voluminous, although perhaps less so than in some of the other areas of investigation discussed at this meeting. Some idea of its extent may be derived from the extensive reviews recently presented by Masland (145, 143). We do not propose, therefore, to be comprehensive in this discussion but have selected a number of areas in which there seems to be either the actuality, or the potential, of demonstration of significant prenatal or perinatal etiologic influences in mental disorders.

We have not interpreted any of the three major words in the assigned title of this article in any limiting sense. Thus "physical" is taken to include biochemical, biologic and any other possible mechanisms of action; "damage" includes all fetal effects that might conceivably be categorized as "mental"; and "fetus" is interpreted in such a way as not to exclude discussion of factors possibly exerting their effects during labor or in the general perinatal period.

Evidence relating mental disorder to factors operating during pregnancy or delivery will be considered at the following levels:

1. Direct evidence that fetuses known to have been exposed to specific agents have a greater frequency of mental disorders than those not exposed.

2. Evidence of unusually high mental disorder rates among special groups believed to have suffered high rates of exposure to deleterious prenatal or perinatal influences the exact nature of which is unknown.

3. Evidence of differences in mental disorder rates between subgroups of the population which may, or may not, be explicable in terms of differences in intra-uterine environmental experience.

This approach requires the discussion of a wide variety of mental abberations under the same heading. The alternative— the subdivision of the paper according to the major varieties of mental abnormality—was initially attempted but abandoned, since many of the studies to be described contain data pertinent to a variety of mental disorders. At the same time, every effort has been made not to confuse methodological evidence relevant to different forms of mental disorder. In particular, quite separate considerations will be taken of the following general categories of disorder:

    1. The chronic brain syndromes, including anencephaly, hydrocephaly, microcephaly, mongolism, cerebral paralysis, etc.

    2. Impairment of function as determined by intelligence tests not associated with a clinical neurological syndrome, referred to for the sake of brevity as mental retardation.

    3. The functional mental disorders, including the psychoses, psychoneuroses, addictions and personality disorders.

DAMAGE DUE TO SPECIFIC AGENTS

The evidence reviewed in this section is of importance not so much because of the numerical significance of the cases of mental disorder that can be ascribed to specific agents, but because of the demonstration that some success has been achieved in identifying such factors and the consequent implication that more remain to be identified.

SPIROCHAETA PALLIDA

Chronic Brain Syndromes. There is no evidence to link intrauterine syphilis infection with the congenital malformations or with the other common brain syndromes. However, congenital syphilis is associated clinically with its own characteristic brain syndromes. The belief that certain neurological signs seen in congenitally syphilitic children are the result of syphilitic infection depends on the similarity of certain of these signs to some of the neurological syndromes of acquired central nervous system syphilis (e.g., "juvenile tabes") or on the specific and characteristic nature of some of the signs (e.g., Argyll Robert-

son pupils). The frequency with which neurological syndromes are seen in prenatally infected children varies with such obvious factors as age of the patients at observation and age at which treatment is begun. Early studies report relatively high frequencies of neurological defects (e.g., 26 per cent of 202 congenital syphilitics (217) but Hallgren and Hollstrom (88) reported only 18 such cases among 219 congenitally syphilitic children of whom the majority received treatment prior to one year of age. When neurological signs are present the frequency of associated mental retardation is very high (e.g., 17 of Hallgren and Hollstrom's 18 cases).

Mental Retardation. The question of whether congenital syphilis is productive of mental retardation in the absence of neurological signs may be considered still open. The question has been attacked in the two classical epidemiologic ways—in case history studies of mentally defective children to determine the frequency of a syphilitic history, and in cohort studies of patients with congenital syphilis to determine the frequency of mental retardation.

From case history studies of mentally retarded children a range of frequency of congenital syphilis between 0.3 per cent (89) and 10 per cent (177) has been reported, with the majority of the values in the larger studies lying between 2 and 5 per cent (17, 124, 233, 50, 165, 175, 204, 135). The problem in the interpretation of these findings is, of course, the lack of suitable comparison groups, since, although the figures seem *a priori* to be higher than the frequencies of congenital syphilis to be expected in general populations of not mentally retarded children, congenitally syphilitic children carry many biologic and social disadvantages besides syphilis. For example, Benda (17) found 38 of the mothers of 76 retarded congenital syphilitic children to be themselves feeble-minded. Thus even where comparisons have been made with the frequency of congenital syphilis or of syphilitic pregnancy in the general population, one cannot be confident that the comparison adequately assesses the biologic effects of prenatal syphilis alone. Such

comparisons as have been made with general population data do not indicate particularly high frequencies of congenital syphilis among the mentally retarded (233, 50). Paddle (165) found a slightly higher frequency of congenital syphilis among mentally retarded children who exhibited epilepsy or physical defects than among uncomplicated cases.

In cohort studies, also, the question of finding a suitable comparison group is crucial and not yet solved. A number of early studies reported high rates of mental retardation among congenitally syphilitic children but did not report on comparison groups of any sort. Some of the types of comparison that have been made in later studies include:

1. Comparison with collateral estimates of the frequency of mental retardation in the general population. Hallgren and Hollstrom (88) in a followup study of 259 cases found a frequency of mental "deficiency" of 15.8 per cent compared to estimates of 1 to 2 per cent in the general population. Mental "subnormality" occurred in 36.7 per cent of the cases compared to population estimates of 7–9 per cent. However, for reasons given above, general population figures do not provide satisfactory comparisons.

2. Comparison according to type of treatment received (usually determined by date of treatment), with the belief that later treatments are generally more effective. Scheer and Stieler (201) and Lenstrup (126) report series in which there is little difference between treatment groups in the frequency of severe mental retardation, but in which the frequency of minor retardation is greater among those receiving the less effective treatment. These differences were not statistically significant. The only authors who have made allowance for differences between treatment groups in age at observation, Hallgren and Hollstrom (88), found in 219 cases no difference in the frequency of mental abnormality between five treatment groups ranging from mercury alone to penicillin plus other forms of treatment.

3. Comparison according to age at first treatment, early treatment being presumably more effective than late. Kundratitz (120) found 8 mentally subnormal among 60 children

treated in infancy compared to 26 mentally subnormal among 66 children treated after infancy. Kiss and Rajka (112) also found a substantial difference between cases treated under 2 years of age and over 2 years, but the number of cases is very small—11 and 34, respectively. Hallgren and Hollstrom (88) noted almost identical frequencies (19 per cent) of mental deficiency among 161 patients treated in the first year of life and 58 treated later.

The latter authors also compared the frequency of mental retardation according to whether or not the mother had received anti-syphilitic treatment during pregnancy. Paradoxically, the frequency of mental deficiency was almost twice as high (28 per cent of 46 cases) in those cases in which the mother had been treated during pregnancy as in those in which she had not (15 per cent of 138 cases). The authors dismiss this difference as being not statistically significant when separate examinations are made according to age at observation, but in the separate age-at-observation categories the difference remains and its lack of statistical significance is probably attributable to the small number of cases in these categories rather than to a reduction of the relative size of the difference. This finding offers a prime reminder of the fact that, in measuring postnatal effects in relation to prenatal influences, our measurement is one of prevalence and not incidence, and is consequently dependent not only on risk of occurrence of the unfavorable event but also on its duration. Thus, if maternal treatment increased the survival of defective children, it might be associated with an increase in prevalence of defective children measured postnatally even though the incidence of children *becoming* defective remained the same.

Even if a difference in mental status according to age at treatment had been demonstrated consistently (and it has not), one would still be faced with the problem of the self-selection of those presenting for early treatment. Hallgren and Hollstrom (88) found no difference between the mental conditions of mothers who received treatment during pregnancy and those who did not. Unfortunately they did not compare the mothers of children receiving treatment in the first year with those of children receiving later treatment in this respect.

4. Comparison according to the presence or absence of signs of congenital syphilis, the infection having presumably been more severe in children showing clinically recognizable signs. As already mentioned, the frequency of mental retardation in children showing neurological signs is very high. This was confirmed in a cohort study by Jenkins *et al.* (102). An interesting study of this type is the comparison by Hollgren and Hollstrom (88) of 328 patients with manifest congenital syphilis in a special home for syphilitic children with 172 patients admitted to the same institution in whom the diagnosis of congenital syphilis was in doubt. The authors state that the frequency of mental deficiency is higher in the first group than in the second. The exact meaning of some of the tables in this publication is obscure, but, so far as we can determine from the data presented, this statement is true only for patients under three years of age. The frequency of "mental subnormality" in patients over three years of age appears to be almost identical in the two groups.

5. Comparison with non-syphilitic siblings. This seems to be the most satisfactory comparison so far considered. Yet, presumably because of practical difficulties, it appears to have been used but once and then in a very small series. Jenkins *et al.* (102) found a lower average I.Q. among 24 cases of congenital syphilitic children than among their siblings, but the difference is not statistically significant.

In summary, we have been unable to find satisfactory evidence that prenatal syphilitic infection is causatively associated with mental retardation in the absence of the more severe neurological syndromes occasionally found in that disease. The virtual extinction of congenital syphilis in the major centers of medical research makes unlikely the provision of more convincing data in the future.

Functional Disorders. The problem of separating the effects of spirochaetal infection from the other concomitants of congenital syphilis is even more serious in interpreting the frequency of the behavior disorders and other functional conditions among such children than in studies of mental retardation.

The association between family disorganization and congenital syphilis has been dramatically shown by Jenkins and Crudim (103) who attribute the high frequency of behavioral disorders among syphilitic children to such concomitant disadvantages rather than to syphilis *per se.* The very high proportion of illegitimate children among such patients (118) is but one example of such a disadvantage.

Hallgren and Hollstrom found a higher frequency of behavior disorders among congenital syphilitic patients who had reached adolescence than among the general population (there is no evidence that similar scales of measurement have been applied) but no evidence of difference between syphilitic children of school age and the "average" school population. There was little difference at any age between their cases of definite and doubtful syphilis. If anything, the patients of adolescent age with questionable diagnoses had a slightly higher frequency of behavioral disorders than the cases with definite diagnoses.

TOXOPLASMA

Chronic Brain Syndromes. The first unequivocal case of human infection with toxoplasma was reported by Wolf *et al.* in 1939 (241), although in retrospect it was considered that four similar cases reported previously could probably be ascribed to this organism. All five cases were infants. Wolf *et al.* believed that the infection occurred *in utero* in view of the early age at onset in all cases (2 days to 7 weeks) and the advanced pathologic state of the central nervous system lesions found at autopsy. Vail (227) believed that, of the 12 cases of toxoplasmic chorioretinitis reported before 1943, 11 were congenital. This view has been upheld by later workers, and has been supported by (a) the observation that in cases of infantile and childhood toxoplasmosis, antibodies can almost invariably be found in maternal blood (198, 136), and (b) the frequent occurrence of malformations such as microcephaly and microphthalmus that indicate infection quite early in pregnancy, and even the occasional prenatal diagnosis of a lesion (hydro-

cephalus) subsequently diagnosed as due to toxoplasma (242). At least one case of isolation of toxoplasma from an abortus has been described (79).

Like most, if not all, of the specific agents known to produce fetal damage, toxoplasma is associated with a characteristic brain syndrome. The characteristic features of congenital toxoplasmosis are chorioretinitis and cerebral calcification. Hydrocephaly, microcephaly, microphthalmus, convulsions, mental deficiency and a variety of serious neurological disorders may be present but are not characteristic. The combination of chorioretinitis and cerebral calcification is associated with toxoplasmic infection in a very high proportion of cases (perhaps in 90 per cent (199)), but children exhibiting one of these signs alone or in combination with the one of the other signs indicated above rarely have positive serological tests (198, 136, 199). It is not likely, therefore, that toxoplasma infection is associated with such brain syndromes as hydrocephaly and microcephaly except when these occur with the more characteristic features of the syndrome.

The proportion of symptomatic human toxoplasmosis that is due to prenatal infection is not known. Most cases in infants and young children are so ascribed on the basis of the extensive damage found (and implied long duration of infection). There is an increasing tendency to ascribe cases in older children to prenatal infection with early quiescence and subsequent recrudescence due perhaps to rupture of a pseudo-cyst (166). This possibility is suggested by the observation that chorioretinitis occurs routinely in childhood toxoplasmosis but is rare in the acquired disease of adults, and the fact that a certain number of congenital cases are undoubtedly quiescent for some time. In adults, for example in the mothers of affected children, toxoplasmic infection appears to be usually symptomless although a few cases with symptoms have been described.

As an asymptomatic infection in adults toxoplasmosis is fairly widespread; for example 5 per cent of a group of adults in North West England showed serum antibodies (136). These cases

must be considered acquired since antibodies are rarely found in normal children (136, 199). The question might therefore be raised as to why prenatal infection is such a comparatively rare occurrence. Sabin and Feldman (199) noted that subsequent children born after a child with toxoplasmosis are normal even though the mothers maintain high titers of antibody. These observations have been explained by MacDonald (136) in terms of trans-placental transmission of maternal antibodies without simultaneous transfer of infection, a phenomenon noted also by others (79, 199). MacDonald suggested that the protective effect of antiserum is extended to the fetus and that the fetus is infected only if the mother is infected during pregnancy or so recently that her antibodies have not yet developed.

Much remains to be clarified regarding the mechanism of toxoplasma infection, the frequency of the asymptomatic congenital disease, and the probability of eventual symptoms among asymptomatic prenatally infected children.

Mental Retardation. As noted, the toxoplasma syndrome is characteristic and it does not seem likely that toxoplasmosis is causally related to undifferentiated mental retardation. Burkinshaw *et al.* (34) performed toxoplasmin tests on 698 mental defectives. The per cent positive increased regularly with age, from zero at ages 0–4 (65 cases) to 58 at ages 50–60 (12 cases). No particular clinical pattern was noted among the 55 positive cases. It was concluded that these were all acquired infections and that such infection was no more common among mental defectives than among the general population.

RUBELLA

Chronic Brain Syndromes. Maternal infection with rubella during the first trimester is also associated with its own characteristic fetal syndrome, comprising congenital cataract, deafness, and, less characteristically, congenital heart disease and microphthalmus. The most critical examination of this association is the summary by Hill *et al.* (93) of their own study and three similar cohort studies (32, 31, 184), which suggest

that the frequency of major fetal defects may be in the order of 50 per cent, 25 per cent, 17 per cent and 0 per cent for infections occurring during the first, second, third, and fourth or later intra-uterine months, respectively.

The brain syndrome established as a likely (though inconstant) part of the rubella syndrome is microcephaly. In reviewing the literature prior to 1949, Swan (219) found 128 cases of microcephaly associated with maternal rubella. Among 9 malformed children with a history of maternal rubella Albaugh (4) found 5 definitely microcephalic. The attribution of the microcephaly to maternal rubella in these cases is lent credence by the fact that 8 of the 9 cases also had the characteristic bilateral cataracts. One case of microcephaly associated with cataract (184) was reported in one of the four cohort studies reviewed by Hill *et al.,* among 50 infants in which rubella occurred in the first trimester.

Other brain syndromes have been reported much less frequently than microcephaly, in spite of the fact that most of them are much more common than microcephaly in general experience. Swan (219) noted in the literature 8 cases of mongolism associated with rubella. In the four cohort studies (104 patients infected at all stages of pregnancy) mongolism and anencephaly occurred once each, although, since the months of pregnancy at which the infection occurred were the fourth and fifth respectively, it seems likely that the association with rubella was fortuitous. Interestingly, these same malformations occurred once each in the 90 controls of a recent study of Siegel and Greenberg (207), but not in the children of 80 women with viral infection during pregnancy. Case history enquiries in two large series of cases of anencephaly did not reveal any case of maternal rubella during pregnancy (189, 44).

Mental Retardation. Mental retardation has been frequently mentioned either as a concomitant of other components of the rubella syndrome or as an isolated result of maternal rubella.

Kirman (111) reported a definite history of maternal rubella in 7 of 791 cases of mental deficiency. In 5 of these the child

also showed cataract, deafness or both. In these five cases the infections occurred in the first trimester of pregnancy. In the other two cases the rubella occurred during the fifth and second month of pregnancy, respectively. No comparison group was used. Of course the characteristic lesions of fetal rubella (blindness and deafness) are such as are likely to be accompanied by apparent mental incapacity, although whether physical brain damage occurs independently of the other lesion is not certain. Mental defect was not a feature noted in the patients in the cohort studies reviewed by Hill *et al.*, but no special effort was made to ascertain this defect. Later studies are planned by at least one of the groups (32). It must be concluded that, at the present time, there is no evidence that prenatal rubella infection predisposes to mental retardation in the absence of the other characteristic features of the syndrome.

OTHER INFECTIONS

Earlier suggestions, based on isolated case reports, that a variety of other infections, including mumps, infective hepatitis, measles and chicken pox, might be associated with fetal defect have not been substantiated by later cohort studies (93, 207). Larger studies are in progress (207).

IONISING RADIATION

Chronic Brain Syndromes. A microcephalic child following deep X-ray therapy of maternal myomata during the first four months of pregnancy was reported by Aschenheim in 1921 (8). In 1929 Murphy (157) assembled reports of 106 cases of maternal pelvic radiation during pregnancy and of 519 women who became pregnant subsequent to irradiation by a review of the literature (155) and by sending a questionnaire to 1,700 gynecologists and radiologists (156). The striking feature of the data is not the high frequency of malformations among the children irradiated *in utero,* since in view of the method of collection of the data it would not have been too surprising if all had been affected, but the predominance among the affected of

one syndrome—among 74 liveborn children irradiated during pregnancy, there were 25 with major malformations of which 17 had microcephaly.

Additional data have been obtained from women who were pregnant at the time of the bombing of Hiroshima and Nagasaki. In Hiroshima 7 infants with microcephaly were born to 11 women exposed within 1,200 meters of the hypocenter but no such cases were seen among 194 women exposed at distances greater than 1,200 meters (186). In Nagasaki one case of definite microcephaly was found among the children of 16 mothers who experienced signs of major radiation injury (245). The difference in rate for the two cities is in part due to the fact that in the Hiroshima study only pregnancies in the first trimester were considered; only 7 of the 16 Nagasaki mothers were in the first trimester. In addition, in Nagasaki, the mean head circumference of the 16 children was significantly smaller than that of the children of mothers who were also within 2,000 meters of the hypocenter but did not have signs of major radiation injury (57 children) and also of that of the children of mothers exposed outside of 2,000 meters (96 children).

It cannot be doubted that large doses of ionising radiation during pregnancy are associated with high risk of microcephaly in the child. However, the rarity of deliberate radiation early in pregnancy makes this an extremely rare cause of congenital malformation at the present time. No brain syndrome other than microcephaly can be convincingly related to *in utero* irradiation, although among the 11 Hiroshima children exposed within 1,200 meters there were two cases of mongolism. This malformation does not feature in the isolated reports of defects following medical radiation, being noted only once by Murphy (157).

Mental Retardation. In addition to the child with microcephaly there were 3 other mentally retarded among the 16 heavily exposed Nagasaki children, but none among the 153 lightly exposed. Otherwise there is no evidence relating ionising radiation to undifferentiated mental retardation in man. In

rats, Furchtgott *et al.* (78) and others (133) have shown that learning ability is seriously affected by both prenatal and neonatal irradiation, and that the severity of the defect is related both to time of intra-uterine exposure and dose of irradiation.

While deliberate radiation during the early months of pregnancy is very rare, all pregnant women experience the normal levels of radioactivity from natural sources. Consequently, evidence of fetal effects associated with exposures to radiation at the levels with which background radiation varies from place to place would be of considerable significance. The recent study of Gentry *et al.* (80) deserves comment therefore, since, while not directly pertinent to mental disorders, if the observations relating to major congenital malformations were confirmed, the next logical step would be similar investigations of less obvious defects, including undifferentiated mental retardation.

Gentry *et al.* noted that, grouping areas of Upstate New York according to the probability of high natural occurrence of radioactive elements in the underlying geologic formations, rates of congenital malformation (as determined from certificates of birth and death) were higher in those areas in which high levels of radioactivity were probable (15.1 malformed infants per 1,000 livebirths) compared with areas in which extensive deposits of radioactive elements were unlikely (12.8 per 1,000). In favor of the hypothesis of direct relationship between background radioactivity and malformation rates are the following: (1) the remarkable consistency of the difference, it being noted for both urban and rural areas, within each of the six standard geographical regions of the State (at least for the rural areas of these regions), and for each of five paternal occupational groups; (2) the relationship is more evident in groups who would be expected to experience heaviest exposure, being more striking in rural than in urban areas and in rural areas in which the water supply is from wells and springs than in rural areas with surface supplies (in fact, rural areas with surface supplies even when located within areas of probable extensive radioactive deposits have rates similar to areas of unlikely deposit);

and (3) examinations of a large number of variables including consanguinity, ethnic background, family reproductive history, etc., are said not to have revealed any alternative explanation of the differences noted, although the nature of these examinations is not detailed. In cautionary vein it should be noted that: (1) the total prevalence rates derived suggest that the sources of data used are identifying only perhaps 50 per cent of the major malformations occurring (depending on one's definition of a major malformation); (2) data on stillbirths are not included, much less those on early fetal deaths, and possible differences in selective loss of deformed infants are therefore not revealed; (3) the correlation between maps of malformation rates and geological formations which seems so obvious to the authors is not at all clear, at least to us; (4) the observations depend essentially on a high malformation rate noted among 15,307 livebirths (259 malformed) in 255 rural communities obtaining water from wells and springs; such communities must be typical in many respects and one cannot feel completely satisfied with general statements about examination for the effects of other variables, particularly when marked differences between the "probable" and "unlikely" areas are evident in certain of the tabulations (for example, of paternal occupation); and (5) it is strange that the relationship should hold for all of nine diagnostic categories of malformation with the exception of mongolism; past studies have pointed more and more to the specificity of action of teratogenic agents in the laboratory animal (237) and to major difference in the epidemiologic characteristics of different malformations in man.

It is clear that this intriguing observation is in urgent need of further investigation, preferably in other geographic areas.

JAUNDICE

Chronic Brain Syndromes. Jaundice of the nuclear centers of the brain associated with neurological symptoms was described in 1875 (163). Cases appeared in the English literature

in 1913 (87) and 1915 (215) but the syndrome was not widely recognized until comparatively recent times; by 1940 only 15 cases had been reported (214). In 1937 Klingman and Carlson, noting 45 instances of severe neonatal jaundice in the histories of 675 children with severe neuromuscular dysfunction, suggested that the syndrome may be more frequent than was generally thought (113). By the end of the next decade individual series of 26 to 37 cases were being reported (228, 41), mostly in association with erythroblastosis fetalis. A very high proportion (about 70 per cent) of obviously affected infants die in the first few days of life (228, 41, 94). The syndrome in surviving infants includes a variety of neurological lesions and mental retardation. Experimental evidence that in rats bilirubin is both the toxic and the staining agent has been provided by Johnson *et al.* (104).

The effect is not strictly a fetal one, since the damage usually occurs in the first day or two of life. This is suggested by the fact that neurological symptoms are not present at birth but develop most commonly on the second day of life (94), kernicterus is not seen in jaundiced infants who die within a few hours of birth (41, 42), and the frequency of kernicterus is apparently greatly reduced by exchange tranfusion (109, 236, 6).

The frequency of this complication of jaundice varies with the type and severity of jaundice reported and the efficacy of the treatment. In erythroblastosis, frequencies of 55 per cent (56), 34 per cent (41), and 12 per cent (228) have been reported. Relating the frequency of kernicterus to the level of the infant's serum bilirubin, Hsia *et al.* (94) report frequencies between zero in the range of serum bilirubin 0–5 mgm per cent to 50 per cent in children with serum bilirubins above 30 mgms per cent. Kelsall and Vos state that in their experience kernicterus has become so rare in incompatible pregnancies treated by induction and exchange transfusion as to be "practically never seen" (109, 110). Armitage and Mollison report frequencies of 41 per cent in 54 infants receiving simple trans-

fusion and 20 per cent in 60 infants receiving exchange trans-
fusion (6). Kernicterus in infants jaundiced for reasons other
than erythroblastosis has been reported by Docter (56) and
Govan and Scott (86).

Mental Retardation. The fact that the signs of kernicterus
vary from mild motor incoordination with normal intellectual
function to severe motor disorders with idiocy suggests that
less obvious defects, including undifferentiated mental retard-
ation, might follow less serious or more localized damage.
Authors with considerable clinical experience have stated that
the signs of kernicterus are so characteristic that the diagnosis
can be made or excluded during the first week of life (228).
However, in a followup study Jones *et al.* (106) found 3
children with definite and 2 with equivocal neurological ab-
normality among 76 erythroblastotic children considered nor-
mal in the neonatal period. Armitage and Mollison also report
4 cases who appeared normal at one month of age and who
either died of kernicterus (one case) or were retarded at the
time of followup (6). Gesell tests were included in the evalu-
ations in the study of Jones *et al.* but results are not given
in the article.

Yannet and Lieberman (247, 248, 249) obtained blood
samples of the mothers of 277 children with I. Q.'s less than 30
and of the children when the mothers were Rh negative. One
hundred fifty-eight of these children fell into recognized diag-
nostic sydromes and 119 were undifferentiated. There were
14 per cent Rh negative mothers in the recognized syndrome
group, which agrees with expectation. This frequency of ma-
ternal Rh negativity should produce an expected maternal-
fetal incompatibility rate of 8.2 per cent, which is close to the
7.6 per cent found. In the undifferentiated group, 22 per cent
of the mothers were Rh negative and 16 per cent of the mother-
child relationships were incompatible. Nineteen cases of moth-
er-child incompatibility were found, compared to 9 expected.
In 6 of these 19 cases, evidence of maternal Rh isoimmuni-
sation was found; all these infants were jaundiced in the

neonatal period. No such evidence was found in the other 13 cases, although the histories were not all adequate to rule out the possibility. It is of interest that all 6 infants with erythroblastosis had significant neurological signs. Histories of the other 13 cases are not given in detail, but it is stated that the physical findings were characterized by absence of signs of central nervous system involvement except for the mental defect. Without the 6 cases of neurological defect the excess of incompatible pregnancies is not statistically significant.

Gerver and Day (81) compared 68 children who had erythroblastosis, with their elder first-born siblings. The 68 patients, did not include any with "obvious motor nerve damage." The 68 patients, at an average age of 4.5 years, had an average I.Q. of 102.7. Their first-born siblings, at an average age of 9.8 years, had an average I.Q. of 114.5, significantly higher than the patients. The authors found no difference between older and younger in 28 pairs of normal siblings who were said to have a similar age difference to that between the patients and their comparison siblings. However, the possibility that a difference between birth orders might contribute to the observed difference between siblings has not been completely ruled out. The relationship between I.Q. and order of birth is complex and, since the two groups were drawn from different sources, the absence of a relationship in one situation does not rule out its existence in the other.

In summary, the evidence to date indicates that if neonatal jaundice is productive of mental defect without neurological signs such cases are probably rare.

ASPHYXIA

In a later section evidence will be presented that a variety of difficulties in labor are likely to be followed by an increased frequency of mental and neurological disorder. This and the subsequent section deal with two specific mechanisms, anoxia and trauma, whereby difficulties of labor might produce their effects. It is, of course, extremely difficult to separate the in-

dependent effects of anoxia and trauma, since infants with one frequently also have the other. For this reason it seemed desirable to consider birth difficulties as a non-specific experience without prejudice as to their mechanism of action. Only studies dealing specifically with anoxia or trauma are discussed in this section.

The problem of the differentiation of anoxic and traumatic effects also arises in pathologic discussion of the problem of birth injury. Thus, although it is generally agreed by pathologists that multiple minor cerebral hemorrhages are associated with cerebral damage following birth injury, Schwartz (205) and other early reporters of these lesions (197) attributed them to mechanical causes. Later pathologists attribute the same lesions to anoxia (188). It seems likely that both mechanisms are involved (48).

Trauma and mechanical asphyxiation are probably the most frequent causes of fetal anoxia. Maternal sedation and anesthesia must also be considered as important causes of fetal anoxia (43, 224, 243), although we have not encountered any studies of the relationship of mental defect to this cause of anoxia specifically.

Chronic Brain Syndromes. Case history studies of series of children with cerebral palsy and epilepsy have indicated high frequencies of neonatal asphyxia. Schreiber reports neonatal asphyxia in 70 per cent of 900 children with neurologic signs (excluding those in whom "inherited defect, postnatal trauma or infection" were suspected) (203). Skatvedt, among 355 patients with cerebral palsy, found 26 per cent with "protracted" initial apnea and a further 18 per cent with asphyxial attacks occurring after initial respiration (200, 208, 209). On the other hand, figures as low as 15 per cent have been suggested as estimates of the proportion of cerebral palsy cases attributable to asphyxia (53). Eastman and DeLeon, in one of the few controlled studies (62), compared 96 children with cerebral palsy with 11,195 surviving normal children. Seventeen per cent of the palsied children did not breathe until

four or more minutes after birth, compared to 0.7 per cent of the normal children. Thirteen per cent of the palsied children did not breathe for six minutes or more, compared to 0.3 per cent of the normal children. These data would suggest an incidence of cerebral palsy forty times higher in those who did not breathe for six minutes or more than in those who breathed within six minutes. Complications of anaesthesia were noted in 4.2 per cent of the cases and 1.0 per cent of the normal births.

It has also been suggested that asphyxia is found frequently in the histories of children with epilepsy (160) and "chronic degenerative disease of the brain" (240), although no control groups were incorporated in these studies, and the evidence is not so striking as in cerebral palsy.

·Windle has produced neurological damage in guinea pigs by constriction of the maternal uterine vessels near term. The more prolonged the asphyxiation the more marked and more persistent were the signs of brain damage. At autopsy capillary hemorrhages were seen, but neuronal damage was encountered even when no capillary extravasations had occurred (238, 239).

It must be accepted that fetal anoxia in the perinatal period is associated with increased risk of neurological damage. However, further quantitation of the relationship and elucidation of the effects of anoxia in the production of minor neurological damage would seem to depend on more detailed cohort studies such as the Cerebral Palsy Collaborative Study of the National Institute of Neurological Diseases and Blindness (144). Particular attention might well be focused on infants who experience anoxia but in whom the probability of physical trauma is not higher than normal.

Fetal defects, mostly skeletal in nature but including anencephaly, have been produced in mice by severe maternal anoxia during pregnancy (98, 97). There is no evidence that such a mechanism operates in man to produce those brain syndromes that are determined early in pregnancy.

Mental Retardation. It has been shown by Windle (238, 239) and Becker (15) that guinea pigs asphyxiated at birth are inferior in maze learning and retention to control litter mates. Two small followup studies in man (of 19 (49) and 61 (35) cases, respectively) have also indicated evidence of poorer intellectual function among asphyxiated infants than among comparison groups. In the latter study the difference was not statistically significant; descriptive groupings were used in place of I.Q. Courville and Marsh state that mental deficiency alone or in combination with neurologic defects is the most common result of clinical neonatal asphyxia (47). They state that most surviving infants show some mental deficit, but the data forming the basis of this experience are not given.

Clearly, here is another area requiring additional data from carefully designed cohort studies.

TRAUMA

While asphyxia may arise from conditions, such as constriction of the cord, that are not associated with trauma, the reverse situation is rare. Consequently it is very difficult to assemble evidence that trauma in itself is productive of neurologic abnormality. Most studies have dealt with methods of delivery in which trauma is probable; these are discussed in a later section. There is remarkably little evidence to indicate the amount of neurological damage following difficult delivery that is directly attributable to the trauma and not to the accompanying asphyxia, or to indicate the possible effects of minor traumatic experiences not associated with gross cerebral hemorrhage.

Nevertheless, physical trauma is *a priori* the most obvious form of fetal damage and its effects can hardly be doubted. Major cerebral hemorrhage associated with tentorial tears and ruptures of the cerebral venous system that can only have been traumatic in origin have been described by many pathologists (197, 37, 68). Such clearly traumatic injuries are associated

particularly with high forceps delivery. Bundesen *et al.* in a large series of autopsies found traumatic cerebral hemorrhages in 55 per cent of cases delivered by mid or high forceps, in 22 per cent of those delivered in low forceps and in 14 per cent of those delivered spontaneously (33). Among 55 cases of subdural hematoma reported by Elvidge and Jackson (68) there were 9 definitely attributable to trauma (as revealed by skull fracture in 6 and tentorial tear in 3) and a further 27 in which the delivery history made the diagnosis of trauma likely.

Cases associated with obvious trauma are, of course, the extreme ones. It is most likely that minor forms of injury also lead to damage. Such, for example, are the clinically well-recognized peripheral nerve palsies associated with specific methods of delivery. In the controlled cerebral palsy study noted above, Eastman and DeLeon (62) noted 26 per cent of the cases exposed to conditions conducive to mechanical trauma as opposed to 8 per cent of the controls.

SPECIFIC NUTRITIONAL DEFICIENCIES

Iodine Deficiency and Thyroid Disorders. The investigation of the relationship between goiter and iodine deficiency is pertinent here insofar as it relates to the etiology of congenital cretinism, a hormonal deficiency associated with severe mental retardation. Mental development is always subnormal in congenital cretinism. The fact that cretins receiving thyroid therapy prior to the age of six months attain somewhat higher intellectual development than those in whom therapy is delayed (213) suggests that some postnatal influence by replacement therapy is possible, but however early such therapy is undertaken a high frequency of mental subnormality still results (213, 85, 232).

It is established that simple goiter, whether congenital or acquired, is associated with dietary iodine deficiency. Other theories explaining the areas of high goiter endemicity, including linking the disease to high background radioactivity in

endemic areas (178, 123), have been discounted in the light of extensive experimental work (72, 141) and human mass therapeutic trials (142, 185, 65), although recent interest in congenital malformations and background radioactivity will, no doubt, renew the attention given this theory.

The fact that congenital cretinism of the endemic form is closely associated geographically with goiter suggests a similar causal mechanism. In Switzerland, Eugster (71, 70) states that his group has never found a case of cretinism in an area free of goiter, whereas in places with a goiter prevalence of over 50 per cent, prevalences of cretinism of 0.6 to 1.0 per cent have been noted. However, it is not clear whether fetal cretinism is directly associated with iodine deficiency (the goiters definitely attributable to iodine deficiency are hyperplastic) or whether the association is operative via maternal physiologic effects produced by the mother's own goiter. The fact that the mothers of cretins, at least in endemic areas (71), are themselves nearly always goiterous suggests that latter possibility. The Swiss experience notwithstanding, congenital cretinism, in both familial and non-familial forms, does occur in areas where iodine intake is adequate (244). However, so far as is known, maternal hyperthyroidism as it occurs in non-goitrous areas is not associated with fetal cretinism or other thyroid abnormalities.

Since the introduction of thiouracil in the treatment of hyperthyroidism, concern has been felt regarding its possible effects on the fetal thyroid. Experimental work suggests reasonable grounds for the concern. Thiouracil given to pregnant rats results in thyroid hyperplasia in the offspring (82). This hyperplasia is prevented if thyroid hormone is administered at the same time (77a), suggesting that maternal thyroid deprivation and not a toxic effect of the drug is responsible. If thiouracil administration is continued (e.g., via the mother's milk) the hyperplasia increases and cretinism eventually results (96, 77b). In man, several cases of congenital goiter following thiouracil treatment during pregnancy have been reported

(1, 29). Only two cases of hyperthyroidism in similar circumstances have been found (154, 67). In both cases the hyperthyroidism was transient; however, in both cases the child was mentally retarded at followup; in one, the child had hydrocephaly thought to be coincidental to the thyroid condition but not the cause of the retardation (154).

At this point, perhaps, mention should be made of the hypothesis linking maternal thyroid disease to fetal mongolism. This hypothesis has appeared in a variety of guises (158, 18), and has been most recently resurrected by Ek (66) who found higher blood protein iodine values among the mothers of a group of mongols than among a haphazardly selected "control" group. The evidence does not seem sufficiently convincing for detailed review, although it cannot be said that the possibility of maternal hormonal imbalance of some type being associated with fetal mongolism has been convincingly eliminated.

Copper. Swayback, a demyelinating disease of lambs, resembling in its pathologic picture Schilder's encephalitis, has been convincingly shown to be the result of maternal copper deficiency during pregnancy (100). It is prevented by the administration of copper to pregnant ewes.

Vitamins. Following the work of Warkany and Nelson on the production of congenital malformation in the rat by maternal Vitamin A deficiency (229, 230, 231), hydrocephaly and other cerebral malformations have been induced by a number of vitamin deficiencies, including riboflavin, folic acid, pantothenic acid, and Vitamin E (159). Hydrocephalus has also been produced in rabbits by maternal Vitamin A deficiency (149). Minor deficits as revealed by maze learning tests, have been noted in the offspring of rats fed on folic acid deficient diets (234).

Although there have been a number of controlled experiments on the results of vitamin supplements in pregnant women (63, 222, 21, 235), some with significant results so far as immediate outcome of pregnancy is concerned (221, 220), the

mental status of the offspring appears to have been considered only once (91). Harrell *et al.* conducted a controlled trial in two populations, one predominantly Negro, the other predominantly white. The treatment groups received: (a) ascorbic acid, (b) ascorbic acid, thiamine, riboflavin, and niacinamide, (c) thiamine and (d) placebo. The results of I.Q. determinations at age 3 years and age 4 years are suggestive but equivocal. In the Negro group (approximately 120 children in each treatment group) the offspring of the supplemented women had significantly higher I.Q's than those of the women receiving the placebo. There were no marked or significant differences between the various supplement groups. In the predominantly white group, which was somewhat larger (approximately 200 children in each treatment group), the placebo group actually had a slightly higher mean I.Q. than any of the treatment groups, but the differences were not significant. Possible reasons for the difference between the results in the two groups include the lower dietary baseline from which supplementation was begun in the Negro group, the slightly longer duration of supplementation in the Negro group (134 days compared to 114 days), and the rural nature of the white population that raised considerable difficulties in ensuring adequacy of administration of the supplements.

Significant increase in I.Q. associated with improvement in general nutrition occurring early in postnatal life has been claimed by Kugelmass *et al.* (119) on the basis of observational studies. Harrell, in a controlled trial, observed improvement in ability in a number of intellectual tasks following thiamine supplementation of the diet (90). These observations are indirectly relevant to consideration of the influence of the prenatal "diet."

Protein. There has been interest in the relationship of maternal dietary protein to immediate outcome of pregnancy (235, 211, 55); once again, none of these studies has been concerned with mental condition of the offspring.

NON-SPECIFIC TRAUMATIC EXPERIENCES
PREMATURITY

Chronic Brain Syndromes. No note will be taken here of the frequent reports of association between prematurity and those chronic brain syndromes that originate in early pregnancy. When such associations exist, as they undoubtedly do, for example in the case of anencephaly and its concomitant hydramnios, it must be considered that the malformation is etiologically related to the prematurity, rather than vice versa.

The high frequency of cerebral palsy and its related disorders among prematurely born infants is well substantiated. It was noted by Little in 1862 (132). The literature has been extensively reviewed by Alm (5) in 1953 and by Polani (187) in 1958. Strong associations have been noted both in case history studies of spastic children (209, 62, 11, 40, 129, 131) and in cohort studies of prematurely born children and various comparison groups (5, 117, 153). The probability of neurological damage increases with the degree of prematurity as measured by birth weight. In a cohort study, Knobloch *et al.* (116) have shown a close association between physical and neurologic defects in premature infants and have suggested that the factors responsible for the increased frequency of cerebral damage in premature infants also have generalized deleterious effects.

In addition to noting a high frequency of children of low birth weight among a series of cases of cerebral palsy, Skatvedt also noted a percentage of children with very high birth weights (over 4,000 gms.) significantly larger than in a group of average hospital births (21.5 per cent compared to 15.5 per cent) (209).

Association of prematurity with convulsive disorders has received less attention. However, the frequency of epilepsy among premature infants does appear to be higher than among children of normal birth weight (5, 22, 58). The most convincing demonstration of this is in the study of Lilienfeld and Pasamanick (129, 171, 128), in which, in both white and

Negro patients, the percentage of children of premature birth was significantly higher among epileptic patients than among a comparison group selected from birth certificates.

Various mechanisms have been postulated to explain the striking association between prematurity and neurological damage. These include physical trauma associated with precipitate delivery, immaturity of the fetal anatomical structures, and higher frequency of abnormal presentations, anoxia initiated by immaturity either of the respiratory musculative (28) or of the respiratory enzyme mechanism (20), and kernicterus associated with greater frequency and severity of erythroblastosis (3) or with physiologic jaundice (2). A developmental mechanism (of unspecified nature) responsible for both neurologic damage and prematurity has been postulated (187), but in view of the many more obvious mechanisms this postulate hardly seems necessary.

Mental Retardation. A number of early studies which, because of either the high proportion of cases for which data are not available (202, 195), or because of the absence of adequate comparison groups (22, 61, 30, 9) did not give convincing results, will not be described although an overall impression of high rates of mental retardation among premature infants is gained from them. Pasamanick and Lilienfeld found a significantly higher proportion of prematurely born infants, both with and without maternal complications, among mentally deficient children than among a comparison group selected from birth registers (172).

Roberts and Asher (192, 10) compared the birth weights of children attending a normal school in a London borough with those of children attending special schools for the retarded and with those of a group of certified mental defectives. Over a wide range of birth weights (about 6 to 10 pounds) there was little variation in the birth weights of the three groups. Below 6 lbs. the retarded groups showed an excess compared to the normal group, which excess increased as the birth weight fell. At the lowest birth weights there were relatively

four times as many cases in the retarded groups as in the normal group. Interestingly, in the light of the observation of Skat-vedt on cerebral palsy (209), there was also a significant excess of retarded children in the birth weight groups over 10.5 pounds.

In a small cohort study in Sweden, Blix and Holmdahl (25) compared 74 premature children with their siblings. The children born prematurely required special classes for mental retardation significantly more frequently than did their siblings. More substantial, and generally more adequately controlled, cohort studies have been reported in the last three years by Knobloch *et al.* (117), Douglas (57) and Drillien (59, 60). In these studies the prematurely born children showed a striking excess of mental retardation as measured by the number of grossly defective on Gesell development tests, or reading, vocabulary, and other mental ability tests. The probability of defect increases with the degree of prematurity (117, 60). The frequency of mental defect is increased in the prematures even in the absence of overt neurological damage, and vice versa (117). In one study, prematures from uncomplicated pregnancies (absence of toxemia, threatened abortion or induction of labor) showed lesser handicap than those from complicated pregnancies (57). On the other hand, Drillien found no definite indication of difference in ability at age two between prematures who had and had not abnormal neonatal signs such as cyanosis or apnea. The fact that, for a given degree of prematurity, first born were less retarded than later born (60) and children of small mothers were less retarded than those of large mothers (57), suggests that the defect is greater among genuinely "immature" deliveries than among infants with physiologically low birth weights.

Functional Disorders. Knobloch and Pasamanick (114) have reported a relationship between birth weight and adaptive behavior in a small group of Negro infants, children with higher birth weights being more advanced than those below median weight. In one of the few studies of prematures fol-

lowed into adult life, Alm (5) found a great many physical and social differences between the prematures and his comparison group but no appreciable differences with respect to frequency of criminality or alcoholism. No undue frequency of prematurity has been found among infants with stuttering (27) or speech disorders (168), or among children with tics (169). On the other hand, it has been suggested that premature infants experience a greater than average frequency of reading (107) and behavior (193, 173) disorders.

Reminiscent of the finding of Roberts and Asher on mental retardation and Skatvedt on cerebral palsy, is the report by Barry (12) of an unusually high proportion of birth weights over 9 lbs. among young adult patients admitted to hospital with psychosis and psychoneurosis. Although the data in this particular study are not convincing, being based on the memories of relatives and not being available for a high proportion of cases, the finding is an interesting one, seeming as it does to associate adult psychiatric illness with a characteristic evident at birth. The observation deserves further investigation.

COMPLICATIONS OF LABOR

Chronic Brain Syndromes. Difficulties of labor associated specifically with fetal anoxia or physical trauma have already been discussed. A great many workers have described the association of mental defect with difficult delivery without consideration of the mechanism whereby the defect is produced.

The clinical syndrome of neurological defect and difficult delivery- is so well recognized that the association of the two in any one child is likely to be considered causative, particularly if the symptoms of neurological defect can be traced to the neonatal period. Among 370 cases of cerebral palsy, Skatvedt (200) found 19.3 per cent of breech presentations, 13.5 per cent of forceps deliveries, and 13.5 per cent precipitate deliveries. The percentage of breech deliveries seems very high, but no comparison group is available to evaluate the noted frequencies of forceps and precipitate deliveries. This author

also notes a high frequency of prolonged labor as reported by the mothers (37 per cent) but other controlled studies have not produced evidence of association of neurological damage with prolonged labor *per se* (62, 108). Ford (75) reports 15 per cent of cases of abnormal labor among 235 children with spastic paralysis, but once again no comparison group is examined. Asher and Schonell, among 221 term deliveries of children with cerebral palsy, found 39 per cent with abnormal deliveries. Twenty-four per cent were forceps deliveries and 15 per cent showed other abnormalities, whereas "normal" rates for these complications were supposed to be about 5 per cent for forceps delivery and 5 per cent for other abnormalities (11).

Dealing specifically with breech presentation, Churchill (39) reports frequencies of 30 per cent idiopathic epilepsy, 8 per cent in cerebral palsy, 5 per cent in mental deficiency and 3 per cent in the general population. From these series, cases "obviously" not originating in the paranatal period were excluded. Znamenacek *et al.* report four times as many cases of birth trauma among breech as among vertex deliveries (251). In the studies of epilepsy (128) and cerebral palsy (127) by Lilienfeld, Parkhurst and Pasamanick that are discussed below, the frequency of breech presentation was no greater in the epileptic children than in the comparison group drawn from birth certificates; nor do the data indicate any greater frequency in the epileptic group of other abnormal presentations or of "dystocia" due to other causes. However, among the children with cerebral palsy, an excess of breech presentations, other malpresentations and a variety of causes of dystocia is evident.

Mental Retardation. Analyzing data on retarded children in Massachusetts public schools, Dayton suggested that abnormal labor was found more frequently in "retarded" than in "defective" children (52). However, the differences noted were very small and the comparison data unsatisfactory. Benaron *et al.* (16) in rather small series (approximately 50

cases in each group) found no statistically significant differences in mental development between groups of children delivered by forceps and those from spontaneous normal deliveries and precipitate labors. A higher frequency of mental retardation was found in the group of precipitate deliveries, but this group is, of course, atypical with respect to birth order, family size and a number of other variables besides rapidity of delivery. In the data of Pasamanick and Lilienfeld (172) (*see* below) the children with undifferentiated mental retardation showed no greater frequency than the comparison group of breech delivery, dystocia due to abnormal pelvis or of other causes of dystocia; a slight increase in the number of malpresentations other than breech is evident, although the data are not separated by parity.

There seems to be little evidence at the present time relating undifferentiated mental retardation to abnormal delivery.

Functional Disorders. In a number of earlier studies, behavioral disorders of childhood were related to history of delivery, but the methods used were crude and do not appear to warrant extended discussion (27, 52, 16, 54). Pasamanick *et al.* (173) compared the pregnancy and labor histories of a group of children with behavior disorders with those of a group of their classmates. The data indicate no appreciably greater frequency of breech delivery or other malpresentations among the patients other than among the comparison group. A somewhat higher frequency of dystocia due to abnormal pelvis occurred among the cases, but the frequency of operative procedures was actually slightly lower among the cases than among the comparison group.

COMPLICATIONS OF PREGNANCY

Since a considerable portion of the evidence linking complications of pregnancy to mental disorders derives from the work of Pasamanick and Lilienfeld and their associates, no attempt will be made in this section of the review to consider the chronic brain syndromes and the other diagnostic groupings

separately. For these authors have stressed the idea of a "continuum of reproductive casualty extending all the way from death to minimum cerebral damage resulting in minor behavioral dysfunction," which might incorporate a number of neuropsychiatric disorders "depending upon the severity, type, or location of the insult" (171, 169, 127, 167). It is consequently difficult to review the work of this group within the arbitrary framework that has been used up to this point.

An identical methodology has been followed in a number of their studies. The method has been to identify from medical care facilities a group of children affected with one of a variety of neuropsychiatric abnormalities—cerebral palsy (127), epilepsy (171, 128), mental retardation (172), behavior disorders (173), speech disorders (168), reading disorders (107), and tics (169). Information was obtained, either from birth certificates, hospital records, or both, as to the frequency of recorded complications of pregnancy or labor. For comparison purposes similar information was abstracted for a group of infants selected from the same series of birth certificates and matched with the patients for race and maternal age and, sometimes, sex and place of delivery. While some elementary data have been presented for specific complications of pregnancy, much of the analysis deals with comparisons of the cases and comparison groups with respect to the frequency of one, two, or more "complications" including conditions as diverse as "non-puerperal complications" and breech presentation. It is clear that the group has in mind a "continuum" of causative agents as well as of end results.

Before reviewing the findings of these studies, it is necessary to express the following reservations about the method:

> 1. The cases are selected by virtue of attending specific medical care facilities and are consequently unrepresentative of the population of the area with respect to socio-economic status, threshold of illness perception, and so on. On the other hand, the comparison groups are representative of the population except with regard to such variables as have been matched, for

example, race and maternal age. The authors have attempted to solve this problem by comparison of cases and comparison groups with respect to census tract of residence; no appreciable differences have apparently been found. However, while census tract of residence is related to socio-economic status the relationship is not always a strong one. Certain of the disorders studied, for example mental retardation, certainly are related to socio-economic status and the absence of difference between cases and comparison groups in a census tract comparison might as easily be attributed to the weakness of the association between census tract and socio-economic status as to the absence of socio-economic differences between the patient and comparison groups.

2. To be included, a "case" must be both born and resident (at the age of ascertainment) in the area studied, whereas a "control" need only be born there. This inevitably leads to differences between the groups with respect to those factors conducive to family mobility—parity, educational status, etc. The matching by maternal age eliminates this difficulty only partially. Nor is the effect of parity on the frequency of complications considered, although separate examinations of parity associations have been conducted in some instances. This criticism does not apply to the study of behavior disorders (173), in which the comparison group was chosen from the schoolmates of the patients.

3. We have some difficulty with the concept that one can group together in a meaningful way a host of diverse maternal "complications" whose only characteristic in common is their appearance on a birth certificate or hospital record, unless their independent effects have first been examined and shown to be similar. So far as possible, therefore, we have preferred to examine the data with respect to individual complications. Unfortunately, the data are not given in the same detail for the individual complications as for the total number of complications of all types.

These theoretical difficulties notwithstanding, this group of studies constitutes our most valuable body of data on the relationship of complications of pregnancy to mental disorder.

The findings with respect to prematurity and the more obvious difficulties of delivery have already been presented. With respect to those complications that might be thought of as influencing fetal development during pregnancy, the following are the most striking findings:

1. Consistent excess of toxemia during the pregnancies producing the affected children. For children with cerebral palsy, epilepsy, behavior disorders, and speech and reading disorders, toxemia was mentioned approximately twice as frequently as in the comparison series. No appreciable difference between patients and controls is evident in the study of mental retardation.

2. An appreciable excess of placenta previa and other causes of bleeding during late pregnancy (the source of information suggests that most of the bleeding reported would be late in pregnancy) is seen for the cases of cerebral palsy, epilepsy, and reading disorders. This relationship appears doubtful for the children with mental deficiency and behavior disorders.

3. Non-puerperal complications appear more frequently in the children with cerebral palsy, mental retardation, and speech or reading disorders than among the comparison groups. This feature is much less striking in the patients with epilepsy or behavior disorders.

Apart from the studies just reviewed, data on the relationship of abnormalities of pregnancy to mental disorder, or to fetal defect in general, are few. Stevenson (216) found a higher frequency of maladjustment in later life among infants judged to be in poor physical condition at the time of birth than in those judged to be in good condition. However, the proportion of infants thought to be in poor condition was not related to the presence or absence of maternal disease during pregnancy, although it was much higher following abnormal delivery. In a case history study of 105 highly selected mentally retarded children, Stolt noted a frequency of toxemia, other maternal complications, and general stress and anxiety higher than among a variety of, again, highly selected, control groups

(218). Turnbull and Walker, following up 155 women leaving hospital after apparently successful treatment of threatened abortion noted a high frequency of ante partum hemorrhage, due in part at least to a high prevalence of placenta previa, and a higher prevalence of fetal defect than among other booked cases (225). In another follow up study of abnormalities noted during the first twelve weeks of pregnancy, McDonald noted a higher frequency of fetal defect following acute febrile illness and active or quiescent tuberculosis but not following threatened abortion (146). Kunnas, in a very brief report on the follow up of 288 children born of toxemic mothers states that the physical and mental development of the children did not differ from normal, but gives no data (121).

Clearly, here is another area in which new data on a large scale are needed.

DESCRIPTIVE EPIDEMIOLOGIC ASSOCIATIONS

There are many descriptive variables, including order of birth, parental age, family size and season of birth, that are believed to indicate early environmental influence in the etiology of those diseases that are associated with them. However, for inclusion in this part of the symposium it is necessary to demonstrate not only that an etiologic influence is environmental in nature but also that its time of operation is prenatal, or at least perinatal. The time of operation of an etiologic factor can be identified in part by the assumption that it must be prior to manifestation of the disease and in part by consideration of the time period during which the descriptive variable involved can be presumed to differentiate between groups of individuals. Thus, any environmental influence in the etiology of the congenital brain syndromes can be presumed prenatal in action by virtue of the first consideration. However, this consideration alone is of little value in the case of the other two major categories of mental disorder since neither is manifest at birth and may in fact not be observed until many years after birth. Association with month of birth is, therefore, a most valuable observation

in these two categories of illness since, under the second consideration, it seems reasonable to believe that month of birth differentiates between the environment of individuals only during intra-uterine life or during the early months of separate existence. It is very difficult to see, for example, why environmental influences acting later than the first year of life should be related to month of birth. On the other hand, order of birth, parental age, and family size are characteristics that influence a person's environment all the way through childhood until he leaves the parental milieu.

MONTH OF BIRTH

Chronic Brain Syndromes. Significant seasonal variation in the frequency of anencephaly has been reported in British data. McKeown and Record, using vital data from Scotland for the years 1939–1946 noted that the stillbirth rate due to anencephaly was lowest in May (1.91 per 1,000 births) and highest in December (3.09 per 1,000) (148). A similar variation was noted for data from Birmingham, in which information on month of conception was also available. Pregnancies conceived during the half year March to August showed a greater prevalence at the time of birth than did those conceived during the half year September to February. The trend was not due to seasonal variation in the parity distribution of births, although it seemed to be more striking for first births. No seasonal variation was evident in data for stillbirths and infant deaths due to spina bifida or hydrocephaly. These relationships were confirmed in later data by Edwards (64), who found no substantial difference between the first born and later born anencephalics in the extent of the seasonal variation.

The largest series of malformations of the central nervous system so far examined in this country, including 326 cases of anencephaly, did not show any seasonal variation for any of the three major diagnostic categories (137). The possibility that the seasonal trend noted in British data is absent in this country requires confirmation. If it is confirmed it is indicative of

a most interesting difference between the two countries in the epidemiologic characteristics of anencephaly.

Three small series of cerebral palsy children, totaling only 339 cases, have been reported from the point of view of month of birth (23, 125, 212) with no consistent trend evident. However, no large series appears to have been examined from this aspect.

Mental Retardation. The relationship between season of birth and intelligence quotient has received a good deal of attention. In 1943, Pintner and Forlano (182) reviewed studies reported prior to that time, including their own extensive studies of school children in New York City (179, 180, 183) and in the Southern Hemisphere (181) and other very large scale studies of school children (26, 84, 74), college students (92, 150, 76, 38), and other adults (73). Among sixteen groups studied, there were ten in which the lowest average intelligence quotients were for persons born in winter[1] and four in which the lowest I.Q.'s were for persons born in autumn. One of the two exceptions to this pattern was the smallest study reported, based on only 337 cases (134). The other was a small but carefully planned Scottish study in which four approximately equal samples of children born on the first days of February, May, August, and November were examined (139). Pintner and Forlano report the results of this study as an exception to the general pattern. However, two separate reports of this study (139, 196) list the average I.Q. for the February-born children as 99.6 and 96.6, respectively, presumably because of a misprint in one of the reports. If the latter figure were in fact the correct one, the February-born would have the lowest average I.Q. of the four groups of children and the results would be consistent with the majority pattern.

Subsequent to 1943, Roberts (190) has published a study based on all children in the town of Bath born during a four-year period, the results of which are generally consistent with

---

[1] December through February in the Northern Hemisphere studies, June through August in the Southern Hemisphere.

the above except for being stated in terms of month of conception rather than of birth. The results of a rather small study of prison inmates by Corsini (46) were not consistent with previous findings, highest average I.Q.'s being found for winter-born and fall-born prisoners.

The relationship between season of birth and intellect has also been studied by examination of the season of birth of mentally retarded children. Blonsky (26) and Pintner and Forlano (181) report an excess of births of mentally retarded children in the winter months, observations that are generally consistent with the general observation of low average I.Q.'s for children born in the winter months. Nolting (162) presents data on approximately 13,000 Dutch and 7,000 British mentally retarded children. In both series there is an excess of births in the months of June and July and a deficiency of births during the period October through January. This finding is not consistent with those of the studies reviewed by Pintner and Forlano. However, the statistical methods used in the various corrections that are applied by Nolting are not clear to us. Furthermore, the data are presented in such a manner and with such an obvious desire to substantiate an hypothesis that we are reluctant to accept these findings as indicative of a difference between American and European experience without independent conformation of the finding in the European data.

Without doubt the most challenging recent observations in this area have been those of Knobloch and Pasamanick (115) who examined the months of birth of children admitted to a school for the mentally retarded over the 36-year period 1913–1948. By comparison with seasonal birth rates in the same State a form of relative risk of first admission was derived according to month of birth. Relative risk was highest for children born in February (1.507 per 1,000) and lowest for those born in August (1.297 per 1,000). This trend is entirely consistent with the studies of I.Q. reviewed by Pintner and Forlano. Furthermore, Knobloch and Pasamanick noted that there was a varia-

ıı

tion in risk of admission from year to year, which they related to average temperature during the summer months. Believing that the eighth to twelfth weeks of gestation are critical ones in the development of the intellect they noted that this period would fall in July for the group of children born in February who showed the highest admission rates. Admission rates for those born in January, February, and March, respectively, were therefore compared for the years following the years in which the temperatures in June, July, and August, respectively, were above and below the median. When the eighth to twelfth weeks of gestation fell in June there was no significant difference in risk of admission between years with temperatures above and below the median. However, when the eighth to twelfth weeks fell in July or August the relative admission risks were 1.658 and 1.519, respectively, when the temperature was above the median compared to 1.276 and 1.206, respectively, in those years when the temperature was below the median. The differences were highly significant and the relationship was consistent in different time periods.

These observations are, in our opinion, among the most significant recent observations in this general area. Their potential significance seems to demand attempts at confirmation in other geographic areas. While the number of cases involved in this particular study is large, the compilation of even larger numbers would enable additional examinations, such as the use of a finer breakdown of temperature range rather than the simple dichotomy used, and more detailed examination of the relationship in different time periods. It would also be desirable to examine the relationship of admission rates to temperature fluctuations during other months than the three chosen, since it is not clear why the eighth to twelfth weeks of gestation should be assumed to be the only ones critical to intellectual development.

Although much more work could be done in exploration of the relationship of I.Q. to season of birth, a review of the work already to hand leaves the distinct impression that a real relationship exists and exhibits a fair degree of consistency from

time to time and from place to place. In explanation, the following possibilities have been offered:

1. Selective seasonal reproduction in relation to intelligence of parents. This possibility was suggested by Goodenough (83) on the basis of observation of a seasonal trend in birth rates for families in the higher occupational classifications and absence of such a trend in the lower occupational groups. The data are not presented in detail and are consequently difficult to evaluate. The possibility is supported in a more satisfactory method by Roberts (190) who noted that:

The seasonal variation in I.Q. noted for a cross-section of children was in one sample virtually eliminated and in another sample actually reversed when examination was restricted to children of the same parents conceived at different seasons, and

The children conceived in winter (whose average I.Q. was highest) had appreciably and significantly fewer siblings than did those conceived in summer.

It is difficult to see why the more intelligent parents should plan to have their children during the hottest months of the year, but nevertheless the arguments offered by Roberts have not been satisfactorily answered. A relationship between season of birth and intelligence of parents may not necessarily be the result of conscious planning. In view of the well-substantiated relationship between sibship size and I.Q., Robert's observation of a lower average sibship size for winter-born children could alone explain the relationship between I.Q. and season of birth. It might also be noted that the absence of a seasonal relationship of birth rate with socio-economic status does not presuppose a similar situation with respect to intelligence of parents.

2. Selective seasonal reproduction related to socio-economic status, the relationship between risk of admission for mental retardation and socio-economic status being generally inverse. This possibility was dismissed by Knobloch and Pasamanick

(115) on the basis of an examination of the month of occurrence of 23,000 births in Baltimore, which is said to have indicated little evidence of differences between socio-economic classes (determined by census tract of residence) in the seasonal distribution of births.

3. Seasonal variation in the parity distribution of births appears not to have been considered by any of these groups of workers. There is a remarkable paucity of vital data on the relationship of season of birth to parity. However, the fact that certain congenital malformations (anencephaly in this country and spina bifida in both this country and in Britain) show strong relationships to parity and yet do not show seasonal variation in frequency suggests that the relationship between parity and season of birth is not sufficiently strong to produce indirect seasonal associations in mental retardation.

4. Temperature effects during critical periods of intra-uterine development. While the direct effects of temperature on mental ability are undoubted (*see*, for example, Mills) (151, 152), it is difficult to see how temperature variation of the order associated with seasonal fluctuation could be responsible for permanent brain damage (particularly that occurring prenatally) except as temperature variation may itself influence other factors such as nutrition or infection.

5. Variation in maternal nutrition associated with variation in environmental temperature during periods of critical intra-uterine development is the explanation favored by Knobloch and Pasamanick for both the seasonal and year-to-year variation noted in their study. A quite specific nutritional factor (maternal Vitamin C deficiency) has been implicated by Nolting. Nolting shows a remarkably high correlation between seasonal variation in maternal Vitamin C levels and his own data on mental retardation, but, as noted, the statistical methods used are unclear and the data on mental retardation are not consistent with data from this country. It seems premature to implicate a specific nutritional deficiency at this time, although the general area of hypothesis is attractive.

Other possible explanations include seasonal variation in maternal complications of pregnancy, such as those noted by

Pasamanick and Knobloch (170), and possible relationship of intellectual development to infections during the early months of life.

Functional Disorders. Tramer (223) noted that among 3,100 patients admitted to a Swiss mental hospital during a 52-year time period there was a relative excess of those born in the months December through March compared to what was believed to be the general seasonal distribution of births. A similar situation has been found by Nolting (161) in an examination of the birth dates of 2,589 schizophrenic patients. The latter also claims to have noted a seasonal variation in the birth dates of 3,000 male psychopaths (162), although the pattern of the variation is not described. These results would seem to require confirmation, and, in view of the simplicity of the information required, it is surprising that more data have not been presented on this subject.

BIRTH ORDER AND MATERNAL AGE

Associations with birth order or maternal age are of significance in that: (1) they indicate the existence of environmental etiologic factors, and (2) they may assist in the identification of such factors. Associations of disease incidence with one or other of these variables rarely have practical implications *per se.* Consequently, the less that is known about the etiology of a disease, the more important knowledge of such an association becomes. In the context of this review, associations with birth order and maternal age seem most significant in the case of (a) congenitally manifest conditions (since it can be assumed that any environmental influence in such conditions is prenatal in origin), and (b) conditions whose etiology is obscure. The congenital malformations fit these criteria most closely. Birth order or maternal age associations for those chronic brain syndromes that originate in the perinatal period, e.g., cerebral palsy and epilepsy, seem of less significance than for those originating early in pregnancy, since a number of recognized etiologic factors in the former group of defects might well be

expected to be associated with order of birth and maternal age
—for example, jaundice, trauma, asphyxia.

In the case of the functional disorders, and to a lesser extent
in the case of mental retardation, associations with order of
birth or maternal age may well be of considerable interest, but
one can have little assurance that the environmental influences
they reveal are prenatal in origin. The functional disorders will
not, therefore, be included in this section of this review.

Chronic Brain Syndromes. The congenital syndromes that
include a "mental" component and that have been demon-
strated to have associations with order of birth or maternal age
are mongolism, anencephaly, and hydrocephaly.

The association of mongolism with age of mother is so strik-
ing that it became evident at least fifty years ago as the result
of clinical observation (206). In spite of the inadequacy of
many of the comparison groups used and the variety of the
sources of data, subsequent studies have invariably confirmed
the presence of this association (101, 194, 122, 24, 19, 13, 69).
In one of the few studies in which a series of mongol children
can be related directly to the population at risk, Carter and
MacCarthy (36) noted a consistent increase in prevalence with
increasing maternal age from zero in the children of mothers
under 20 and 0.29 per 1,000 in the age groups 20–29, to 26 per
1,000 in the children of mothers aged 45 or more. Early writers
also commented frequently on the tendency of mongols to occur
at the end of large families. However, Penrose (174) showed
that this apparent association with birth order results from the
association of mongolism with maternal age and the close cor-
relation between birth order and maternal age. In fact, it has
been shown recently that, if maternal age is held constant, there
is a slightly higher risk of mongolism in the first born compared
to second and later born (164, 210).

Penrose (176) examined a small series of cases of malforma-
tions of the central nervous system by the Greenwood-Yule
method and found increasing risk with increasing maternal age
and birth order; maternal age seemed to have the closer asso-

ciation. In a much larger series, Record and McKeown (189) assembled sufficient material for adequate examination of the separate diagnoses and also obtained information on the birth rank and maternal age distribution of the related population. Prevalence of anencephalus and spina bifida was found to be higher in first births and in births after the sixth than in the intermediate birth orders. No association with maternal age was evident for these two malformations when the influence of birth order was held constant. On the other hand, hydrocephalus showed increasing prevalence with maternal age, and little independent effect of birth order. Generally similar findings have been reported in examinations of data for stillbirths in Scotland (189, 138, 64), except that it is not possible to examine the effects of the two variables independently in these data and the pattern of birth order association for anencephalus suggests a gradual increase in risk with birth order (after the initial drop from first to second births), rather than the low plateau between second and sixth births suggested by the Birmingham data.

There seems to be some variation in these patterns from place to place and time to time. Thus, a small series of anencephalics reported from Ireland indicated a higher frequency in the children of mothers over 30 years of age but no significant independent effect of birth order (39). In a study of children born with malformations of the central nervous system in Rhode Island between 1936 and 1952, the general patterns were similar to those noted by Record and McKeown, but the difference in risk of anencephaly between first and second births was generally smaller than that noted in Birmingham and in the latest time period examined (1948–1952) was non-existent (99).

In our present state of knowledge it does not seem profitable to speculate on the interpretation of these associations, beyond noting broad categories of variables that may be related to birth order and/or maternal age. These include a variety of social and economic circumstances, changes in maternal anatomical and physiologic characteristics, and frequency of maternal dis-

ease. It should be stressed that these associations have been demonstrated in prevalence, not incidence, data, and are susceptible to variation not only through changes in incidence (occurrence of the disease) but also through changes in duration (i.e., differences in the survival of affected and not affected children).

Associations of epilepsy and cerebral palsy with birth order and maternal age have been studied by Beall and Stanton (14), Yannet (246), and Lilienfeld and Parkhurst (127), among others. The latter authors have pointed out that the patterns of association are similar to those that have been found for perinatal mortality, for example by Yerushalmy *et al.* (250). This similarity forms part of the basis of their concept of a "continuum" of fetal damage.

Mental Retardation. The results of examination of the birth rank distribution of series of mental defectives have not been consistent. Thus, Dayton (51), in data on 10,455 retarded Massachusetts children found no association with maternal age, and no association with birth order when the evident effect of family size was held constant. Turner and Penrose (226) suggested that the relationship might vary with the severity of the defect—"low-grade" deficiency being a characteristic of the first-born and "high-grade" deficiency occurring more frequently in the higher birth orders. Malzberg (140) found a higher than expected proportion of first born, but not the excess in the later birth ranks noted by Turner and Penrose. Most recently, Lilienfeld and Pasamanick (130) found a striking increase in frequency with increasing birth rank which was present in each maternal age group; an association with maternal age was also present but was not clear cut when parity was held constant. No account was taken by these workers of the association between family size and mental defect.

The relationship between family size and intelligence quotient is a strong one, and must be considered in studying the relationship of I.Q. in "normal" children to birth order and parental age. This may be done by comparing individual family

sizes (147) or, more satisfactorily, by comparing sibship pairs and other combinations from the same families. When the latter method has been followed, some early studies suggested that average I.Q. is higher for the later born than for the first born (7, 45), but in later studies no significant effects of maternal age or birth order have been demonstrated (105, 95, 191).

OTHER DESCRIPTIVE CHARACTERISTICS

Mention should be made of two other characteristics of the epidemiology of anencephalus that strongly suggest the existence of important environmental determinants of an unknown nature. One of these is the striking secular change in prevalence. Both in England and Wales (138) and in Rhode Island (137) the frequency of this malformation was almost half as high in the years around 1950 than it had been in the early war years. Such changes cannot be explained by any genetic mechanism. Secondly, the marked relationship of anencephaly to social class noted by Edwards (64) is strong evidence of environmental etiology.

CONCLUSIONS

Direct evidence of damage due to fetus-environment interaction exists with respect to the chronic brain syndromes that originate in the perinatal period. The nature of the environmental agents that are productive of brain syndromes during the early months of pregnancy is to a large extent unknown, although there is indirect evidence that they exist and some few rare toxic agents have been identified. Evidence that the functional disorders may be related to prenatal damage is yet to be found.

A great deal of descriptive (i.e., survey) work remains to be done in the field of congenital malformations to formulate hypotheses applicable to man. A vast amount of experimental work in this area has been of value from the point of view of biologic understanding but has not produced a single hypothesis capable of substantiation in human data.

In the field of perinatal brain syndromes the type of research

most lacking appears to be the identification of the possible minor effects of lower exposures to agents whose major effects are well documented. Such research requires carefully planned and documented observation of cohorts of exposed individuals. Such studies must be large and will necessarily be expensive, but no alternative method of securing this type of information is available.

In the area of mental retardation a number of challenging hypotheses linking mental defect to general environmental circumstances during the early months of pregnancy await test. In addition to direct tests of, for example, the influence of temperature and/or maternal nutrition, further descriptive studies would appear to be indicated in order to test the generalizability of the observations on which the hypotheses are based.

In a search for evidence that the functional disorders might be influenced by prenatal circumstances, it would seem desirable to check thoroughly those observations that link functional disorders to characteristics evident at birth. The possibility that functional disorders may be related to month of birth or birth weight are facts that have a theoretical significance far deeper than that which is immediately apparent.

REFERENCES

1. Aaron, H. H.; Schneierson, S. J.; Siegel, E.: Goiter in Newborn Infant Due to Mother's Ingestion of Propylthiouracil. *Journal of the American Medical Association,* October 29, 1955, 159: 848–850.

2. Aidin, R.; Corner, B.; Tovey, G.: Kernicterus and Prematurity. *Lancet,* June 24, 1950, 1: 1153–1154.

3. Allen, F. H., Jr.; Diamond, L. K.; Vaughan, V. C., iii: Erythroblastosis Fetalis; Prevention of Kernicterus. *American Journal of Diseases of Children,* November, 1950, 80: 779–791.

4. Albaugh, C. H.: Congenital Anomalies Following Maternal Rubella in Early Weeks of Pregnancy, With Special Emphasis on Congenital Cataract. *Journal of the American Medical Association,* November 10, 1945, 129: 719–723.

5. Alm, I.: The Long-Term Prognosis for Prematurely Born Children. A Follow-up Study of 999 Premature Boys Born in Wedlock and of 1,002 Controls. *Acta paediatrica,* 1953, 42, Suppl. 94 (whole issue).

6. Armitage, P.; Mollison, P. L.: Further Analysis of Controlled Trials of Treatment of Haemolytic Disease of Newborn. *Journal of Obstetrics and Gynaecology of the British Empire,* October, 1953, 60: 605–620.

7. Arthur, G.: The Relation of IQ to Position in Family. *The Journal of Educational Psychology*, November, 1926, 17: 541–550.

8. Aschenheim, E.: Schädigung einer menschlichen Frucht Durch Röntgenstrahlen. *Archiv für Kinderheilkunde*, 1921, 68: 131–140.

9. Asher, C.: Prognosis of Immaturity. *British Medical Journal*, May 25, 1946, 1: 793–796.

10. Asher, C.; Roberts, J. A. F.: Study on Birthweight and Intelligence. *British Journal of Social Medicine*, April, 1949, 3: 56–68.

11. Asher, P.; Schonell, F. E.: Survey of 400 Cases of Cerebral Palsy in Childhood. *Archives of Disease in Childhood*, December, 1950, 25: 360–379.

12. Barry, H., Jr.: Abnormally Large Birth Weights of Psychiatric Patients. *Archives of Neurology and Psychiatry*, January, 1947, 57: 98–101.

13. Beall, G.; Stanton, R. G.: Reduction in Number of Mongolian Defectives—Result of Family Limitation. *Canadian Journal of Public Health*, January, 1945, 36: 33–37.

14. Beall, G.; Stanton, R. G.: Relationship Between Epilepsy and Maternal Age. *Human Biology*, February, 1946, 18: 49–60.

15. Becker, R. F.: Learning Ability After Asphyxiation at Birth, Especially as it Concerns the Guinea Pig. *in* NEUROLOGICAL AND PSYCHOLOGICAL DEFICITS OF ASPHYXIA NEONATORUM. Springfield, Illinois, Thomas, 1958. 336 pp.; 44–54.

16. Benaron, H. B. W., *et al.*: Remote Effects of Prolonged Labor with Forceps Delivery, Precipitate Labor with Spontaneous Delivery, and Natural Labor with Spontaneous Delivery on Child. *American Journal of Obstetrics and Gynecology*, September, 1953, 66: 551–565.

17. Benda, C. E.: Congenital Syphilis in Mental Deficiency. *American Journal of Mental Deficiency*, July, 1942, 47: 40–48.

18. Benda, C. E.: MONGOLISM AND CRETINISM. Second Edition. New York, Grune & Stratton, 1949. 316 pp.

19. Benda, C. E.; Dayton, N. A.; Prouty, R. A.: On Etiology and Prevention of Mongolism. *The American Journal of Psychiatry*, May, 1943, 99: 822–834.

20. Berfenstam, R.: Studies on Carbonic Anhydrase Activity in Children; Enzyme Activity in Blood of Infants and Children of Different Ages, Particularly in Premature Infants. *Acta paediatrica*, 1952, 41: 32–52.

21. Berry, K.; Wiehl, D. G.: Experiment in Diet Education During Pregnancy. *The Milbank Memorial Fund Quarterly*, April, 1952, 30: 119–151.

22. Beskow, B.: Mental Disturbances in Premature Children at School Age. *Acta paediatrica*, 1949, 37: 125–149.

23. Bevan, R. T.: Birthdays of Spastics. Letter to the Editor. *Lancet*, February 16, 1957, 1: 375.

24. Bleyer, A.: Role of Advanced Maternal Age in Causing Mongolism; Study of 2,822 Cases. *American Journal of Diseases of Children*, January, 1938, 55: 79–92.

25. Blix, H.; Holmdahl, K.: A Follow-up Examination of Small Premature Infants at School Age. *Acta paediatrica*, July, 1955, 55, Suppl. 103: 113–114.

26. Blonsky, P. P.: Früh- und Spätjahrkinder. *Jahrbuch für Kinderheilkunde und physische Erziehung*, May, 1929, 124: 115–120.

27. Boland, J. L., Jr.: Type of Birth as Related to Stuttering. *The Journal of Speech and Hearing Disorders*, March, 1951, 16: 40–43.

28. Boutourline-Young, H.; Boutourline-Young, E.: Alveolar Carbon Dioxide Levels in Pregnant, Parturient and Lactating Subjects. *Journal of Obstetrics and Gynaecology of the British Empire,* August, 1956, 63: 509–528.

29. Branch, L. I.; Tuthill, S. W.: Goiters in Twins Resulting From Propylthiouracil Given During Pregnancy. *Annals of Internal Medicine,* January, 1957, 46: 145–148.

30. Brander, T.: Studien über die Entwicklung der Intelligenz bei Frühgeborenen Kindern. Beiträge zur Kenntnis der Entstehung insbesondere leichterer Grade der exogen bedingten Unterbegabung. Societas Scientiarum Fennica. Berlin: Friedländer; Helsingfors: Akad. Buchh., 1936.

31. Brawner, D. L.: Maternal Rubella: Results Following Epidemic. *Journal of the Medical Association of Georgia,* September, 1955, 44: 451–454.

32. Brown, C. M.; Nathan, B. J.: Maternal Rubella and Congenital Defects. *Lancet,* May 8, 1954, 1: 975–976.

33. Bundesen, H. N., et al.: Progress in Reduction of Needless Neonatal Deaths; Challenge to Health Officer and Medical Profession. *Journal of the American Medical Association,* March 15, 1952, 148: 907–917.

34. Burkinshaw, J.; Kirman, B. H.; Sorsby, A.: Toxoplasmosis in Relation to Mental Deficiency. *British Medical Journal,* March 28, 1953, 1: 702–704.

35. Campbell, W. A. B.; Cheeseman, E. A.; Kilpatrick, A. W.: Effects of Neonatal Asphyxia on Physical and Mental Development. *Archives of Disease in Childhood,* December, 1950, 25: 351–359.

36. Carter, C.; MacCarthy, D.: Incidence of Mongolism and Its Diagnosis in Newborn. *British Journal of Social Medicine,* April, 1951, 5: 83–90.

37. Chase, W. H.: Anatomical Study of Subdural Haemorrhage Associated with Tentorial Splitting in Newborn. *Surgery, Gynecology and Obstetrics,* July, 1930, 51: 31–41.

38. Chenoweth, L. B.; Canning, R. G.: Relation of Season of Birth to Certain Attributes of Students. *Human Biology,* December, 1941, 13: 533–540.

39. Churchill, J. A.: The Relationship of Idiopathic Epilepsy and Breech Delivery. *Transactions of the American Neurological Association,* 1957, 134–136.

40. Churchill, J. A.: The Relationship of Little's Disease to Premature Birth. *Journal of Diseases of Children,* July, 1958, 96: 32–39.

41. Claireaux, A.: Haemolytic Disease of Newborn: Clinical-Pathological Study of 157 Cases; Nuclear Jaundice (Kernicterus). *Archives of Disease in Childhood,* March, 1950, 25: 61–80.

42. Claireaux, A. E.; Cole, P. G.; Lathe, G. H.: Icterus of Brain in Newborn. *Lancet,* December 12, 1953, 2: 1226–1230.

43. Clifford, S. H.; Irving, F. C.: Analgesia, Anesthesia and Newborn Infant. *Surgery, Gynecology and Obstetrics,* July, 1937, 65: 23–29.

44. Coffey, V. P.; Jessop, W. J. E.: A Study of 137 Cases of Anencephaly. *British Journal of Preventive & Social Medicine,* October, 1957, 11: 174–180.

45. Commins, W. D.: Intelligence of Later Born. *School and Society,* April 23, 1927, 25: 488.

46. Corsini, R.: Season of Birth and Mental Ability of Prison Inmates. *The Journal of Social Psychology,* February, 1946, 23: 65–72.

47. Courville, C. B.; Marsh, C.: Neonatal Asphyxia; Its Encephalic Residuals and Mechanism of Their Production. *Bulletin of the Los Angeles Neurological Society*, September–December, 1944. 9: 121–134.

48. Courville, C. B.: Contributions to Study of Cerebral Anoxia; Asphyxia in Legend, Folklore and History. *Bulletin of the Los Angeles Neurological Society*, September, 1950, 15: 99–128.

49. Darke, R. A.: Late Effects of Severe Asphyxia Neonatorum; Preliminary Report. *The Journal of Pediatrics*, February, 1944, 24: 148–158.

50. Dayton, N. A.: Congenital Syphilis as Cause of Mental Deficiency; Statistics. *Boston Medical and Surgical Journal*, October 8, 1925, 193: 668–671.

51. Dayton, N. A.: Order of Birth and Size of Family; Survey of 10,455 Retarded Children in Public Schools of Massachusetts. *The American Journal of Psychiatry*, May, 1929, 8: 979–1006.

52. Dayton, N. A.: Abnormal Labor as Etiological Factor in Mental Deficiency and Other Associated Conditions; Analysis of 20,473 Cases. *New England Journal of Medicine*, August 28, 1930, 203: 398–413.

53. Deaver, G. G.: Present-day Concepts of Cerebral Palsy. *International Record of Medicine*, June, 1956, 169: 339–344.

54. Despert, J. L.: Anxiety, Phobias, and Fears in Young Children, With Special Reference to Prenatal, Natal, and Neonatal Factors. *The Nervous Child*, January, 1946, 5: 8–24.

55. Dieckmann, W. J., *et al.*: Observations on Protein Intake and Health of Mother and Baby; I. Clinical and Laboratory Findings. *Journal of the American Dietetic Association*, December, 1951, 27: 1046–1052.

56. Docter, J. M.: Kernicterus; Neurological Sequelae of Erythroblastosis Fetalis. *The Journal of Pediatrics*, October, 1945, 27: 327–334.

57. Douglas, J. W. B.: Mental Ability and School Achievement of Premature Children at 8 Years of Age. *British Medical Journal*, May 26, 1956, 1: 1210–1214.

58. Douglas, J. W. B.; Mogford, C.: Health of Premature Children from Birth to 4 Years. *British Medical Journal*, April 4, 1953, 1: 748–754.

59. Drillien, C. M.: A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. I. Introduction. *Archives of Disease in Childhood*, October, 1958, 33: 417–422.

60. Drillien, C. M.: A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. III: Mental Development. *Archives of Disease in Childhood*, February, 1959, 34: 37–45.

61. Duyzings, A. J. M.: Über die Frühgeburt und das zu früh geborene Kind. *Archiv für Gynäkologie*, 1935, 159: 524–536.

62. Eastman, N. J.; DeLeon, M.: Etiology of Cerebral Palsy. *American Journal of Obstetrics and Gynecology*, May, 1955, 69: 950–961.

63. Ebbs, J. H.; Tisdall, F. F.; Scott, W. A.: Influence of Prenatal Diet on Mother and Child. *The Journal of Nutrition*, November, 1941, 22: 515–526.

64. Edwards, J. H.: Congenital Malformations of the Central Nervous System in Scotland. *British Journal of Preventive & Social Medicine*, July, 1958, 12: 115–130.

65. Eggenberger, H.; Messerli, F. M.: Theory and Results of Prophylaxis of Endemic Goiter in Switzerland. *Transactions of the Third International Goiter Conference and American Association for the Study of Goiter*, 1938: 64–67.

66. Ek, J. I.: Thyroid Function in Mothers of Mongoloid Infants. *Acta paediatrica*, January, 1959, 48: 33–42.

67. Elphinstone, N.: Thiouracil in Pregnancy, Its Effect on Foetus. *Lancet*, June 27, 1953, 1: 1281–1284.

68. Elvidge, A. R.; Jackson, I. J.: Subdural Hematoma and Effusion in Infants; Review of 55 Cases. *American Journal of Diseases of Children*, November, 1949, 78: 635–658.

69. Engler, M.: MONGOLISM. Baltimore, Williams & Wilkins, 1949, 208 pp.

70. Eugster, J.: Endemic Goiter and Cretinism Investigation Based on More Than 15,000 Clinical Observations. *Transactions of the Third International Goiter Conference and American Association for the Study of Goiter*, 1938: 130–138.

71. Eugster, J.: Zur Pathogenese des endemischen Kretinismus. Beobachtungen an Müttern von Kretinen. *Schweizerische medizinische Wochenscrift*, July 16, 1938, 68: 820–821.

72. Fenger, F.: On the Iodine and Phosphorus Contents, Size and Physiological Activity of the Fetal Thyroid Gland. *The Journal of Biological Chemistry*, 1913, 14: 397–405.

73. Fialkin, H. N.; Beckman, R. O.: The Influence of Month of Birth on the Intelligence Test Scores of Adults. *The Pedagogical Seminary and Journal of Genetic Psychology*, 1938, 52: 203–209.

74. Fitt, A. B.: SEASONAL INFLUENCE ON GROWTH, FUNCTION AND INHERITANCE. Wellington, New Zealand Council for Educational Research, 1941, 182 pp.

75. Ford, F. R.: Cerebral Birth Injuries and Their Results. *Medicine*, May, 1926, 5: 121–194.

76. Forlano, G.; Ehrlich, V. Z.: Month and Season of Birth in Relation to Intelligence, Introversion-Extraversion, and Inferiority Feelings. *The Journal of Educational Psychology*, January, 1941, 32: 1–12.

77a. Freiesleben, E.; Kjerulf-Jensen, K.: Effect of Thiouracil Derivatives on Fetuses and Infants. *Nordisk medicin*, December 6, 1946, 32: 2811–2812.

77b. Freiesleben, E.; Kjerulf-Jensen, K.: Effect of Thiouracil Derivatives on Fetuses and Infants. *The Journal of Clinical Endocrinology*, January, 1947, 7: 47–51.

78. Furchtgott, E.; Echols, M.; Openshaw, J. W.: Maze Learning in Pre- and Neonatally- X-irradiated Rats. *Journal of Comparative and Physiological Psychology*, April, 1958, 51: 178–180.

79. Gard, S.; Magnusson, J. H.; Hagberg, E.: Congenital Toxoplasmosis. *Acta paediatrica*, 1952, 41: 15–31.

80. Gentry, J. T.: An Epidemiological Study of Congenital Malformations in New York State. *American Journal of Public Health and the Nation's Health*, April, 1959, 49: 497–513.

81. Gerver, J. M.; Day, R. L.: Intelligence Quotient of Children Who Have Recovered from Erythroblastosis Fetalis. *The Journal of Pediatrics*, March, 1950, 36: 342–348.

82. Goldsmith, E. D.; Gordon, A. S.; Charipper, H. A.: Analysis of Effects of Continued Thiourea Treatment in Pregnancy and on Development of Offspring in Rat. *American Journal of Obstetrics and Gynecology*, February, 1945, 49: 197–206.

83. Goodenough, F. L.: Intelligence and Month of Birth. *Psychological Bulletin*, July, 1940, 37: 442.

84. Goodenough, F. L.: Month of Birth as Related to Socio-economic Status of Parents. *The Pedagogical Seminary and Journal of Genetic Psychology,* September, 1941, 59: 65–76.

85. Gordon, M. B.: Childhood Myxedema (Sporadic Cretinism) in the United States. A Critical Review of the Literature. *Transactions of The Third International Goiter Conference and American Association for the Study of Goiter,* 1938, 114–129.

86. Govan, A. D. T.; Scott, J. M.: Kernicterus and Prematurity. *Lancet,* March 28, 1953, 1: 611–614.

87. Guthrie, L.: Case of Kernikterus Associated With Choreiform Movements. *Proceedings of the Royal Society of Medicine,* January 23, 1914, 7: 86–88.

88. Hallgren, B.; Hollstrom, E.: Congenital Syphilis; Follow-up Study with Reference to Mental Abnormalities. *Acta psychiatrica et neurologica scandinavica,* Suppl. 93, 1–81, 1954.

89. Hansmann, G. H.: Syphilis, with Special Reference to Incidence in Relationship to Age Groups and Status of Therapy at Date of Infection. *Journal of the American Medical Association,* May 6, 1939, 22: 1796–1798.

90. Harrell, R. F.: Mental Response to Added Thiamine. *The Journal of Nutrition,* March, 1946, 31: 283–298.

91. Harrell, R. F.; Woodyard, E. R.; Gates, A. I.: Influence of Vitamin Supplementation of Diets of Pregnant and Lactating Women on Intelligence of Their Offspring. *Metabolism: Clinical and Experimental,* September, 1956, 5: 555–562.

92. Held, O. C.: The Influence of Month of Birth on the Intelligence of College Freshmen. *The Pedagocical Seminary and Journal of Genetic Psychology,* September, 1940, 57: 211–217.

93. Hill, A. B. *et al.:* Virus Diseases in Pregnancy and Congenital Defects. *British Journal of Preventive & Social Medicine,* January, 1958, 12: 1–7.

94. Hsia, D. Y. Y. *et al.:* Erythroblastosis Fetalis: Studies of Serum Bilirubin in Relation to Kernicterus. *New England Journal of Medicine,* October 30, 1952, 247: 668–671.

95. Hsiao, H. H.: Status of First-Born, With Special Reference to Intelligence. *Genetic Psychological Monographs,* January–February, 1931, 9: 1–118.

96. Hughes, A. M.: Cretinism in Rats Induced by Thiouracil. *Endocrinology: Bulletin of the Association for the Study of Internal Secretions,* January, 1944, 34: 69–76.

97. Ingalls, T. H.; Curley, F. J.: Principles Governing the Genesis of Congenital Malformations Induced in Mice by Hypoxia. *New England Journal of Medicine,* December 5, 1957, 257: 1121–1127.

98. Ingalls, T. H.; Curley, F. J.; Prindle, R. A.: Anoxia as Cause of Fetal Death and Congenital Defect in Mouse. *Journal of Diseases of Children,* July, 1950, 80: 34–45.

99. Ingalls, T. H.; Pugh, T. F.; MacMahon, B.: Incidence of Anencephalus, Spina Bifida, and Hydrocephalus Related to Birth Rank and Maternal Age. *British Journal of Preventive & Social Medicine,* January, 1954, 8: 17–23.

100. Innes, J. R. M.: Swayback: Demyelinating Disease of Lambs with Affinities to Schilder's Encephalitis and its Prevention by Copper. *Journal of Neurology and Psychiatry,* October, 1939, 2: 323–334.

101. Jenkins, R. L.: Etiology of Mongolism. *Journal of Diseases of Children,* March, 1933, 45: 506–519.

102. Jenkins, R. I.; Brown, A. W.; Cisler, L. E.: Influence of Syphilis on Intelligence of Children. *Journal of Diseases of Children,* August, 1940, 60: 341–351.

103. Jenkins, R. L.; Crudim, M.: Behavior Problems in Children with Syphilis: Relation to Juvenile Paresis. *American Journal of Orthopsychiatry,* October, 1941, 11: 752–769.

104. Johnson, L. *et al.:* Kernicterus in Rats with an Inherited Deficiency of Glucuronyl Transferase. *Journal of Diseases of Children,* May, 1959, 97: 591–608.

105. Jones, H. E.; Hsiao, H. H.: A Preliminary Study of Intelligence as a Function of Birth Order. *The Pedagocical Seminary and Journal of Genetic Psychology,* 1928, 35: 428–433.

106. Jones, M. H., *et al.:* Longitudinal Study of Incidence of Central Nervous System Damage Following Erythroblastosis Fetalis. *Pediatrics,* October, 1954, 14: 346–350.

107. Kawi, A. A.; Pasamanick, B.: Association of Factors of Pregnancy Disorders in Childhood. *Journal of the American Medical Association,* March 22, 1958, 166: 1420–1423.

108. Keith, H. M.; Norval, M. A.: Neurologic Lesions in the Newly Born Infant. I. Preliminary Study; II. Role of Prolonged Labor, Asphyxia and Delayed Respiration. *Pediatrics,* August, 1950, 6: 229–243.

109. Kelsall, G. A.; Vos, G. H.: Premature Induction of Labour in Treatment of Haemolytic Disease of Newborn. *Lancet,* July 23, 1955, 2: 161–164.

110. Kelsall, G. A.; Watson, J. R. H.; Vos, G. H.: Haemolytic Disease of the Newborn. The Fate of 246 Rhesus-Incompatible Pregnancies. *Lancet,* December 21, 1957, 2: 1255–1258.

111. Kirman, B. H.: Rubella as Cause of Mental Deficiency. *Lancet,* November 26, 1955, 2: 1113–1115.

112. Kiss, P.; Rajka, T.: Intelligenzprüfungen an Kindern mit angeborener Syphilis. *Archiv für Kinderheilkunde,* 1934, 102: 25–36.

113. Klingman, W. O.; Carlson, E. R.: Cerebral Sequelae of Severe Jaundice in Newborn. *Bulletin of the Neurological Institute of New York,* August, 1937, 6: 228–232.

114. Knobloch, H.; Pasamanick, B.: Further Observations on the Behavioral Development of Negro Children. *The Pedagogical Seminary and Journal of Genetic Psychology,* 1953, 83: 137–157.

115. Knobloch, H.; Pasamanick, B.: Seasonal Variation in the Births of the Mentally Deficient. *American Journal of Public Health and the Nation's Health,* September, 1958, 48: 1201–1208.

116. Knobloch, H., *et al.:* The Effect of Prematurity on Health and Growth. *American Journal of Public Health and the Nation's Health,* September, 1959, 49: 1164–1173.

117. Knobloch, H., *et al.:* Neuropsychiatric Sequelae of Prematurity; Longitudinal Study. *Journal of the American Medical Association,* June 16, 1956, 161: 581–585.

118. Krag, P.; Dalsgaard-Nielsen, E.: Studies on Congenital Syphilis Diagnosed in Period of 1935–1939; Diagnosis of Congenital Syphilis. *Acta pathologica et microbiologica scandinavica,* 1944, 21: 264.

119. Kugelmass, I. N.; Poull, L. E.; Samuel, E. L.: Natural Improvement of Child Mentality. *American Journal of the Medical Sciences,* November, 1944, 208: 631–633.

120. Kundratitz, K.: Zur Intensivbehandlung der kongenitalen Lues. *Archiv für Kinderheilkunde,* July 25, 1930, 91: 21–33.

121. Kunnas, M.: A Follow-up Study of Children Born of Mothers Suffering from Toxaemia of Pregnancy. *Acta paediatrica,* Suppl. 103, July, 1955, 44: 57.

122. Lahdensuu, S.: Über Vorkommen und Ätiologie der Idiotia mongoloidea im Lichte des in Finnland gesammelten Materials. *Acta paediatrica,* 1937, 21: 256–288.

123. Lang, T.: Bisherige Ergebnisse meiner Messungen und Tierversuche in Hinblick auf die Radioaktivitatshypothese des endemichen Kropfes und Kretinismus. *Transactions of the Third International Goiter Conference and American Association for the Study of Goiter,* 1938, p. 20–29.

124. Lawrence, J. S.: Congenital Syphilis in Institutional Children. *Journal of the American Medical Association,* February 25, 1922, 78: 566–568.

125. Lee, H. B.: Birthdays of Spastics. Letter to the Editor, *Lancet,* February 23, 1957, 1: 430.

126. Lenstrup, E.: Two Hundred and Fifty Cases of Congenital Syphilis. *Ugeskrift for laeger,* February 28, 1935, 97: 268–270.

127. Lilienfeld, A. M.; Parkhurst, E.: Study of Association of Factors of Pregnancy and Parturition with Development of Cerebral Palsy; Preliminary Report. *American Journal of Hygiene,* May, 1951, 53: 262–282.

128. Lilienfeld, A. M.; Pasamanick, B.: Association of Maternal and Fetal Factors with Development of Epilepsy; Abnormalities in Prenatal and Paranatal Periods. *Journal of the American Medical Association,* June 19, 1954, 155: 719–724.

129. Lilienfeld, A. M.; Pasamanick, B.: Association of Maternal and Fetal Factors with Development of Cerebral Palsy and Epilepsy. *American Journal of Obstetrics and Gynecology,* July, 1955, 70: 93–101.

130. Lilienfeld, A. M.; Pasamanick, B.: Association of Maternal and Fetal Factors With Development of Mental Deficiency; Relationship to Maternal Age, Birth Order, Previous Reproductive Loss and Degree of Mental Deficiency. *American Journal of Mental Deficiency,* January, 1956, 60: 557–569.

131. Lilienfeld, A. M.; Pasamanick, B.; Rogers, M.: Relationship Between Pregnancy Experience and Development of Certain Neuropsychiatric Disorders in Childhood. *American Journal of Public Health and the Nation's Health,* May, 1955, 45: 637–643.

132. Little, W. J.: On the Influence of Abnormal Parturition, Difficult Labours, Premature Birth, and Asphyxia Neonatorum, on the Mental and Physical Condition of the Child, Especially in Relation to Deformities. *In* Obstetrical Society of London, *Transactions,* 1861, 3: 293–344. London, Longman, Green, Longman, and Roberts, 1862. 480 pp.

133. Levinson, B.: Effects of Fetal Irradiation on Learning. *The Journal of Comparative and Physiological Psychology,* April, 1952, 45: 140–145.

134. Looft, C.: Les Enfants Printaniers et les Enfants d'Automne. Leur Evolution d'Intelligence. *Acta paediatrica,* 1934, 15: 381–395.

135. Lurie, L. A.; Greenebaum, J. V.; Brandes, E. B.: Syphilis as Factor in Behavior Disorders of Children. *Urologic and Cutaneous Review,* February, 1941, 45: 108–111.

136. Macdonald, Alexander: Incidence of Toxoplasma Infection in North-west England; Transmission of Antibody from Mother to Foetus. *Lancet,* November 18, 1950, 2: 560–562.

137. MacMahon, B.; Pugh, T. F.; Ingalls, T. H.: Anencephalus, Spina Bifida,

and Hydrocephalus; Incidence Related to Sex, Race, and Season of Birth, and Incidence in Siblings. *British Journal of Preventive & Social Medicine*, October, 1953, 7: 211–219.

138. MacMahon, B.; Record, R. G.; McKeown, T.: Secular Changes in Incidence of Malformations of Central Nervous System. *British Journal of Social Medicine*, October, 1951, 5: 254–258.

139. MacMeeken, A. M.: THE INTELLIGENCE OF A REPRESENTATIVE GROUP OF SCOTTISH CHILDREN. London: University Press, 1939.

140. Malzberg, B.: Statistical Aspects of Mental Deficiency Due to Birth Traumas. *American Journal of Mental Deficiency*, April, 1950, 54: 427–433.

141. Marine, D.: Etiology and Prevention of Simple Goiter. *Medicine*, November, 1924, 3: 453–479.

142. Marine, D.; Kimball, O. P.: Prevention of Simple Goiter in Man. *Archives of Internal Medicine*, June, 1920, 25: 661.

143. Masland, R. L.: The Prevention of Mental Retardation; a Survey of Research. *Journal of Diseases of Children*, January, 1958, 95: 3–111.

144. Masland, R. L.: A Collaborative Project for the Study of Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Childhood. Presented at the 86th Annual Meeting of the American Public Health Association, St. Louis, Missouri, 1958.

145. Masland, R. L.; Sarason, S. B.; Gladwin, T.: MENTAL SUBNORMALITY: BIOLOGICAL, PSYCHOLOGICAL, AND CULTURAL FACTORS. New York, Basic Books, 1958. 442 pp.

146. McDonald, A. D.: Maternal Health and Congenital Defect. *The New England Journal of Medicine*, April 17, 1958, 258: 767–773.

147. McFadden, J. H.: A Further Note on the Differential IQ's of Siblings. *The Journal of Applied Psychology*, 1929, 13: 86–91.

148. McKeown, T.; Record, R. G.: Seasonal Incidence of Congenital Malformations of Central Nervous System. *Lancet*, January 27, 1951, 1: 192–196.

149. Millen, J. W.; Woollam, D. H. M.; Lamming, G. E.: Hydrocephalus Associated with Deficiency of Vitamin A. *Lancet*, December 12, 1953, 2: 1234–1236.

150. Mills, C. A.: Mental and Physical Development as Influenced by Season of Conception. *Human Biology*, September, 1941, 13: 378–389.

151. Mills, C. A.: Influence of Environmental Temperatures on Warm-Blooded Animals. *Annals of the New York Academy of Sciences*, June 15, 1945, 46: 97–105.

152. Mills, C. A.: Temperature Dominance Over Human Life. *Science*, September 16, 1949, 110: 267–271.

153. Mohr, G. J.; Bartelme, P.: Mental and Physical Development of Children Prematurely Born; Preliminary Report on Mental Development. *Journal of Diseases of Children*, November, 1930, 40: 1000–1015.

154. Morris, D.: Transient Hypothyroidism in Newborn Infant. *Lancet*, June 27, 1953, 1: 1284–1285.

155. Murphy, D. P.: Ovarian Irradiation; Its Effect on the Health of Subsequent Children. Review of Literature, Experimental and Clinical, With a Report of Three-Hundred and Twenty Human Pregnancies. *Surgery, Gynecology and Obstetrics*, August, 1928, 47: 201–215.

156. Murphy, D. P.: Ovarian Irradiation and Health of Subsequent Child; Review of More than 200 Previously Unreported Pregnancies in Women Subjected to

Pelvic Irradiation. *Surgery, Gynecology and Obstetrics,* June, 1929, 48: 766–779.

157. Murphy, D. P.: Outcome of 625 Pregnancies in Women Subjected to Pelvic Radium or Roentgen Irradiation. *American Journal of Obstetrics and Gynecology,* August, 1929, 18: 179–187.

158. Myers, C. R.: An Application of the Control Group Method to the Problem of the Etiology of Mongolism. *The Journal of Psycho-Asthenics,* June, 1937–June, 1938, 43, No. 1: 142–150. (Proceedings of the American Association on Mental Deficiency, 62nd Annual Session held at Richmond, Va., April 20–23, 1938.)

159. Nelson, M. M.: Production of Congenital Anomalies in Mammals by Maternal Dietary Deficiencies. *Pediatrics,* April, 1957, 19: 764–776.

160. Nielsen, J. M.: Etiology of Idiopathic Epilepsy. *Bulletin of the Los Angeles Neurological Society,* September–December, 1946, 11: 97–101.

161. Nolting, W. J. J. de S.: Further Communication on the Connection Between Schizophrenia and the Month in Which the Subjects Are Born. (Translated title.) *Nederlandsch tijdschrift voor geneeskunde,* June, 1939, 88: 3219.

162. Nolting, W. J. J. de S.: Considerations Regarding a Possible Relation Between the Vitamin C Content of the Blood of Pregnant Women and Schizophrenia, Debilitas Mentis and Psychopathia. *Folia Psychiatrica, Neurologica et Neurochirurgica, Neerlandica,* August, 1955, 58: 285–295.

163. Orth, J.: Ueber das Vorkommen von Bilirubinkrystallen bei neugobornen Kindern. *Archiv für pathologische Anatomie und Physiologie klinische Medicin,* May 25, 1875, 63: 447– 462.

164. Øster, J.: Mongolism; a clinicogenealogical investigation comprising 526 mongols living on seeland and neighboring islands in denmark. Copenhagen, Danish Science Press, 1953, 205 pp.

165. Paddle, K. C. L.: Congenital Syphilis in Mental Defective Adults. *The Journal of Neurology and Psychopathology,* October, 1934, 15: 147–159.

166. Parks, M. M.: Ophthalmological Suspicion of Unrecognized Congenital Toxoplasmosis. *Clinical Proceedings of the Children's Hospital, (Washington, D. C.),* May, 1959, 15: 125–126.

167. Pasamanick, B.: Patterns of Research in Mental Hygiene. *Psychiatric Quarterly,* October, 1952, 26: 577–589.

168. Pasamanick, B.; Constantinou, F. K.; Lilienfeld, A. M.: Pregnancy Experience and Development of Childhood Speech Disorders; Epidemiologic Study of Association with Maternal and Fetal Factors. *Journal of Diseases of Children,* February, 1956, 91: 113–118.

169. Pasamanick, B.; Kawi, A.: Study of Association of Prenatal and Paranatal Factors with Development of Tics in Children; Preliminary Investigation. *The Journal of Pediatrics,* May, 1956, 48: 596–601.

170. Pasamanick, B.; Knobloch, H.: Seasonal Variation in Complications of Pregnancy. *Obstetrics and Gynecology,* July, 1958, 12: 110–112.

171. Pasamanick, B.; Lilienfeld, A. M.: Maternal and Fetal Factors in Development of Epilepsy; Relationship to some Clinical Features of Epilepsy. *Neurology,* February, 1955, 5: 77–83.

172. Pasamanick, B.; Lilienfeld, A. M.: Association of Maternal and Fetal Factors with Development of Mental Deficiency; Abnormalities in Prenatal and Paranatal Periods. *Journal of the American Medical Association,* September 17, 1955, 159: 155–160.

173. Pasamanick, B.; Rogers, M. E.; Lilienfeld, A. M.: Pregnancy Experience and Development of Behavior Disorder in Children. *The American Journal of Psychiatry,* February, 1956, 112: 613–618.

174. Penrose, L. S.: Method of Separating Relative Aetiological Effects of Birth Order and Maternal Age, With Special Reference to Mongolian Imbecility. *Annals of Eugenics,* October, 1934, 6: 108–127.

175. Penrose, L. S.: A CLINICAL AND GENETIC STUDY OF 1280 CASES OF MENTAL DEFECT. Medical Research Council, Special Report Series, No. 229. London, His Majesty's Stationery Office, 1938, 159 pp.

176. Penrose, L. S.: Familial Data on 144 Cases of Anencephaly, Spina Bifida and Congenital Hydrocephaly. *Annals of Eugenics,* August, 1946, 13: 73–98.

177. Penrose, L. S.: THE BIOLOGY OF MENTAL DEFECT. New York, Grune & Stratton, 1949, 285 pp.

178. Pighini, G.: Radioemanazione (Radon) ed Alterazionai stumosa della Tiroide. *Transactions of the Third International Goiter Conference and American Association for the Study of Goiter,* 1938: 30–32.

179. Pintner, R.: Intelligence and Month of Birth. *Journal of Applied Psychology,* April, 1931, 15: 149–154.

180. Pintner, R.; Forlano, G.: The Influence of Month of Birth on Intelligence Quotients. *The Journal of Educational Psychology,* November, 1933, 24: 561–584.

181. Pintner, R.; Forlano, G.: Season of Birth and Intelligence. *The Pedagogical Seminary and Journal of Genetic Psychology,* June, 1939, 54: 353–358.

182. Pintner, R.; Forlano, G.: Season of Birth and Mental Differences. *Psychological Bulletin,* January, 1943, 40: 25–35.

183. Pintner, R.; Maller, J. B.: Month of Birth and Average Intelligence Among Different Ethnic Groups. *The Pedagogical Seminary and Journal of Genetic Psychology,* 1937, 50: 91–107.

184. Pitt, David B.: Congenital Malformations and Maternal Rubella. *The Medical Journal of Australia,* February 23, 1957, 1: 233–239.

185. Plass, E. D.; Yoakam, W. A.: Basal Metabolism Studies in Normal Pregnant Women with Normal and Pathologic Thyroid Glands. *American Journal of Obstetrics and Gynecology,* October, 1929, 18: 556–568.

186. Plummer, G. W.: Anomalies Occurring in Children Exposed in Utero to Atomic Bomb in Hiroshima. *Pediatrics,* December, 1952, 10: 687–692.

187. Polani, P. E.: Prematurity and "Cerebral Palsy." *British Medical Journal,* December 20, 1958, 2: 1497–1499.

188. Potter, E. L.: PATHOLOGY OF THE FETUS AND THE NEWBORN. Chicago, Year Book Publishers, 1952, 574 pp.

189. Record, R. G.; McKeown, T.: Congenital Malformations of Central Nervous System; Survey of 930 Cases. *British Journal of Social Medicine,* October, 1949, 3: 183–219.

190. Roberts, J. A. F.: Intelligence and Season of Conception. *British Medical Journal,* March 4, 1944, 1: 320–322.

191. Roberts, J. A. F.: Birth Order, Maternal Age and Intelligence. With Particular Reference to a Possible Effect on the Association Between Intelligence and Family Size. *The British Journal of Psychology, Statistical Section,* 1947, 1: 35–51.

192. Roberts, J. A. F.; Asher, C.: Birthweight and Intelligence. *American Journal of Mental Deficiency,* July, 1949, 54: 87–92.

193. Rogers, M. E.; Lilienfeld, A. M.; Pasamanick, B.: Prenatal and Paranatal Factors in Development of Childhood Behavior Disorders. *Acta psychiatrica et neurologica scandinavica*, Suppl. 102, 1955, 1–157.

194. Rosanoff, A. J.; Handy, L. M.: Etiology of Mongolism, With Special Reference to Its Occurrence in Twins. *Journal of Diseases of Children*, October, 1934, 48: 764–779.

195. Rosanoff, A. J.; Inman-Kane, C. V.: Relation of Premature and Underweight Condition at Birth to Mental Deficiency. *The American Journal of Psychiatry*, January, 1934, 13: 829–852.

196. Rusk, R. R.: The Intelligence of Scottish Children. Yearbook, National Society for the Study of Education, 1940. 39 (II): 269–273.

197. Rydberg, E.: Cerebral Injury in New-born Children Consequent on Birth Trauma; with an Inquiry into Normal and Pathological Anatomy of Neuroglia. *Acta pathologica et microbiologica scandinavica*, Suppl. 10, 1932: 1–247.

198. Sabin, A. B.: Toxoplasma Neutralizing Antibody in Human Beings and Morbid Conditions Associated with It. *Proceedings of the Society for Experimental Biology and Medicine*, October, 1942, 51: 6–10.

199. Sabin, A. B.; Feldman, H. A.: Chorioretinopathy Associated with Other Evidence of Cerebral Damage in Childhood; Syndrome of Unknown Etiology Separable from Congenital Toxoplasmosis. *The Journal of Pediatrics*, September, 1949, 35: 296–309.

200. Salomonsen, L.; Skatvedt, M.: The Clinical Features and Etiology of Cerebral Palsy. *Acta paediatrica*, Suppl. 103, July, 1955, 44: 17–20.

201. Scheer, K.; Stieler, M.: Wirkt die starke Behandlung der Lues congenita ungünstig auf die geistigen Fähigkeiten? *Jahrbuch für Kinderheilkunde und physische Erziehung*, April, 1927, 115: 332–247.

202. Schöberlein, W.: Zur Frage der Entwicklung der Unreifgeborenen. *Monatsschrift für Kinderheilkunde*, 1938, 76: 80–106.

203. Schreiber, F.: Neurologic Sequelae of Paranatal Asphyxia. *The Journal of Pediatrics*, March, 1940, 16: 297–309.

204. Schulte, H.: Klinischer Beitrag zur Kenntnis der kongenital-luischen Störungen des Zentralnervensystems. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, 1940, 169: 250–272.

205. Schwartz, P.: Die traumatischen Schädigungen des Zentralnervensystems durch die Geburt. Anatomische Untersuchungen. *Ergebnisse der inneren Medizin und Kinderheilkunde*, 1927, 31: 165–372.

206. Shuttleworth, G. E.: Mongolian Imbecility. *The British Medical Journal*, September 11, 1909, 2: 661–665.

207. Siegel, M.; Greenberg, M.: Virus Diseases in Pregnancy and Their Effects on the Fetus. Preliminary Report of a Controlled, Prospective Study. *American Journal of Obstetrics and Gynecology*, March, 1959, 77: 620–627.

208. Skatvedt, M.: Some Figures to Throw Light on Aetiological Factors in a Cerebral Palsy Material of Altogether 320 Patients. *Acta paediatrica*, Suppl. 103, July, 1955, 44: 121.

209. Skatvedt, M.: Cerebral Palsy. A Clinical Study of 370 Cases. *Acta paediatrica*, Suppl. 111, July, 1958, 46: 1–96.

210. Smith, A.; Record, R. G.: Maternal Age and Birth Rank in Aetiology of Mongolism. *British Journal of Preventive & Social Medicine*, January, 1955, 9: 51–55.

211. Smith, C. A.: Effects of Maternal Undernutrition Upon Newborn Infant in Holland. *The Journal of Pediatrics,* March, 1947, 30: 229–243.

212. Smith, C. S.: Birthdays of Spastics. Letter to the Editor. *Lancet,* March 2, 1957, 1: 478.

213. Smith, D. W.; Blizzard, R. M.; Wilkins, L.: The Mental Prognosis in Hypothyroidism of Infancy and Childhood; a Review of 128 Cases. *Pediatrics,* June, 1957, 19: 1011–1022.

214. Sobel, I. P.; Zucker, J. M.: Icterus Gravis Neonatorum; End Results of Syndrome of Nuclear Jaundice. *The Journal of Pediatrics,* April, 1940, 16: 445–455.

215. Spiller, W. G.: Severe Jaundice in the Newborn Child a Cause of Spastic Cerebral Diplegia. *The American Journal of the Medical Sciences,* March, 1915, 149: 345–350.

216. Stevenson, S. S.: Paranatal Factors Affecting Adjustment in Childhood. *Pediatrics,* August, 1948, 2: 154–161.

217. Stokes, J. H.: MODERN CLINICAL SYPHILOLOGY CASE STUDIES. London: W. B. Saunders, 1934, 1400 pp. Second Edition, 1936.

218. Stott, D. H.: Physical and Mental Handicaps Following a Disturbed Pregnancy. *The Lancet,* May 18, 1957, 1: 1006–1011.

219. Swan, C.: Rubella in Pregnancy as Aetiological Factor in Congenital Malformation, Stillbirth, Miscarriage and Abortion. *Journal of Obstetrics and Gynaecology of the British Empire,* June , 1949, 56: 341–363; August, 1949, 56: 591–605.

220. Tompkins, W. T.; Mitchell, R. M.; Wiehl, D. G.: Maternal and Newborn Nutrition Studies at Philadelphia Lying-in Hospital. Maternal Studies II. Prematurity and Maternal Nutrition. *In* THE PROMOTION OF MATERNAL AND NEWBORN HEALTH. New York: Milbank Memorial Fund, 1955, 229 pp.: 25–50.

221. Tompkins, W. T.; Wiehl, D. G.: Maternal and Newborn Nutrition Studies at Philadelphia Lying-in Hospital. Maternal Studies III. Toxemia and Maternal Nutrition. *In* THE PROMOTION OF MATERNAL AND NEWBORN HEALTH. New York: Milbank Memorial Fund, 1955, 229 pp.: 62–79.

222. Toverud, G.: Influence of Nutrition on Course of Pregnancy. *Milbank Memorial Fund Quarterly,* January, 1950, 28: 7–24.

223. Tramer, M.: Über die biologische Bedeutung des Geburtsmonates, insbesondere für die Psychoseerkrankung. *Schweizer Archiv für Neurologie und Psychiatrie,* 1929, 24: 17–24.

224. Tucker, B. E.; Benaron, H. B. W.: Immediate Effects of Prolonged Labor with Forceps Delivery, Precipitate Labor with Spontaneous Delivery, and Natural Labor with Spontaneous Delivery on Child. *American Journal of Obstetrics and Gynecology,* September, 1953, 66: 540–550.

225. Turnbull, E. P. N.; Walker, J.: Outcome of Pregnancy Complicated by Threatened Abortion. *Journal of Obstetrics and Gynaecology of the British Empire,* August, 1956, 63: 553–559.

226. Turner, F. D.; Penrose, L. S.: Investigation Into Position in Family of Mental Defectives. *Journal of Mental Science,* July, 1931, 77: 512–524.

227. Vail, D.: Chorioretinitis Associated with Toxoplasma. *Proceedings of the Royal Society of Medicine,* October, 1943, 36: 629–632.

228. Vaughan, V. C., III; Allen, F. H., Jr.; Diamond, L. K.: Erythroblastosis Fetalis; Further Observations on Kernicterus. *Pediatrics,* November, 1950, 6: 706–716.

229. Warkany, J.; Nelson, R. C.: Appearance of Skeletal Abnormalities in Offspring of Rats Reared on Deficient Diet. *Science,* October 25, 1940, 92: 383–384.

230. Warkany, J.; Nelson, R. C.: Skeletal Abnormalities in Offspring of Rats Reared on Deficient Diets. *Anatomical Record,* January 25, 1941, 79: 83–100.

231. Warkany, J.; Nelson, R. C.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency. *The Journal of Nutrition*, April, 1942, 23: 321-333.

232. Warkany, J.; Wilson, J. G.: Prenatal Effects of Nutrition on the Development of the Nervous System. Association for Research in Nervous and Mental Disease, *Proceedings*. 1953, 33: 76–83. [Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns. (D. Hooker and C. C. Hare, Eds.) Baltimore, Williams and Wilkins, 1954, 425 pp. Chap. 6.]

233. Weiss, M.; Izgur, L.: Syphilis as a Factor in the Etiology of Mental Deficiency. *Journal of the American Medical Association*, January, 1924, 82: 12–14.

234. Whitley, J. R.; O'Dell, B. L.; Hogan, A. G.: Effect of Diet on Maze Learning in Second-Generation Rats. Folic Acid Deficiency. *The Journal of Nutrition*, September 10, 1951, 45: 153–160.

235. Wiehl, D. G.; Tompkins, W. T.: Maternal and Newborn Nutrition Studies at Philadelphia Lying-in Hospital. Maternal Studies I. Method of Study and Description of Sample. *In* The Promotion of Maternal and Newborn Health. New York: Milbank Memorial Fund, 1955, 229 pp.: 1–24.

236. Wiener, A. S.: Treatment of Erythroblastosis Fetalis by Exchange Transfusion. *Postgraduate Medicine*, January, 1950, 7: 1–10.

237. Wilson, J. G.: Is There Specificity of Action in Experimental Teratogenesis? *Pediatrics*, April, 1957, 19: 755–763.

238. Windle, W. F.: Structural and Functional Alterations in Brain Following Neonatal Asphyxia. *Psychosomatic Medicine*, April, 1944, 6: 155–156.

239. Windle, W. F.: Brain Damage in the Guinea Pig After Asphyxia Neonatorum, *In* Neurological and Psychological Deficits of Asphyxia Neonatorum, With Consideration of Use of Primates for Experimental Investigations. Springfield, Illinois, Thomas, 1958, 336 pp.: 1–43.

240. Wolf, A.; Cowen, D.: The Cerebral Atrophies and Encephalomalacias of Infancy and Childhood. Association for Research in Nervous and Mental Disease, *Proceedings*, 1954, 34: 199–330. [Neurology and Psychiatry in Childhood (R. McIntosh and C. C. Hare, Eds.) Baltimore, Williams and Wilkins, 1954, 504 pp. Chap. ii.]

241. Wolf, A.; Cowen, D.; Paige, B. H.; Toxoplasmic Encephalomyelitis; New Case of Granulomatous Encephalomyelitis Due to a Protozoon. *American Journal of Pathology*, November, 1939, 15: 657–694.

242. Wolf, A.; Cowen, D.; Paige, B. H.: Fetal Encephalomyelitis: Prenatal Inception of Infantile Toxoplasmosis. *Science*, June 6, 1941, 93: 548–549.

243. Wolff, J. R.; Roter, A.: Repeat Cesarean Section. *American Journal of Obstetrics and Gynecology*, May, 1955, 69: 1070–1082.

244. Wright, S. W. *et al.*: Etiologic Factors in Mental Deficiency; Errors of Metabolism that may lead to Mental Deficiency. *Journal of Diseases of Children*, May, 1958, 95: 541–562.

245. Yamazaki, J. N.; Wright, S. W.; Wright, P. M.: Outcome of Pregnancy in Women Exposed to Atomic Bomb in Nagasaki. *Journal of Diseases of Children*, April, 1954, 87: 448–463.

246. Yannet, H.: Etiology of Congenital Cerebral Palsy; Statistical and Clinical Study. *The Journal of Pediatrics*, January, 1944, 24: 38–45.

247. Yannet, H.: Importance of Rh Factor in Mental Deficiency; Preliminary Report. *Bulletin of the New York Academy of Medicine*, September, 1944, 20: 512–514.

248. Yannet, H.; Lieberman, R.: Rh Factor in Etiology of Mental Deficiency. *American Journal of Mental Deficiency,* October, 1944, 49: 133–137.

249. Yannet, H.; Lieberman, R.: Central Nervous System Complications Associated with Kernicterus. *Journal of the American Medical Association,* February 9, 1946, 130: 335–340.

250. Yerushalmy, J.; Palmer, C. E.; Kramer, M.: Studies in Childbirth Mortality; Age and Parity as Factors in Puerperal Fatality. *Public Health Reports,* July 5, 1940, 55: 1195–1220.

251. Znamenacek, K.: A Clinical Study of Perinatal Trauma in Newborn Infants. I. Analysis of Surviving Infants. *Études Néonatales,* June, 1957, 6: 79–88.

DISCUSSION

DR. PAUL M. DENSEN: I am really very awed by the amount of work that must have gone into this kind of a review and grateful for the opportunity to go over it.

I have taken the purpose of my assignment from Dr. Boudreau's letter asking me to attend this meeting, in which he said that the function of the discussant was to raise issues that the paper suggests in the field generally, and, possibly if we had the time and interest, we might take up a few items of special interest to the discussant.

Consequently, I consider my role to be more or less that of a catalyst, to try to get you talking about the paper rather than to do most of the talking myself.

I have approached the problem of reviewing this paper on the assumption that the kinds of evidence that are needed in this field are just the same kinds of evidence that are needed in any other field, but that the order of probabilities may be very different in the mental health field than you have in some of the physical sciences.

Since the field of mental health is one with which I am not too well acquainted, I tried the usual trick of going back to something with which I was a little bit more familiar.

There were two main points that struck me in reading over Dr. MacMahon's review. One of them is a basic question which, it seems to me, applies to Dr. Böök's paper as well as Dr. MacMahon's and perhaps to many of the other papers in our symposium. This is related to this kind of question:

When you psychiatrists say: "This is a schizophrenic individual and that one is an individual with psychosis of one kind or another, and this is a case of functional disorder of one kind or another," what is the probability that another physician—another psychiatrist

—looking at these same individuals is going to say that this individual is a schizophrenic, etc.?
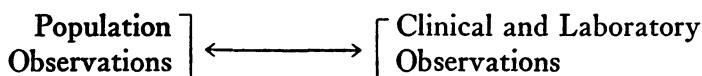
In other words, how reliable do you think your diagnoses are in this field, and have there been any studies of this? I think this is a rather basic problem.

This is not to say that you necessarily are going to have orders of probability that are like .99 or anything of the kind, but I think it is important to know something about where the variation exists among different individuals in making these kinds of diagnoses and what kind of things they tend to vary on.

I wonder whether there have been any studies of this kind in the field. I am reminded here very much of the kind of thing that has happened in tuberculosis, in some of the reports of Yerushalmy and Birkelo when they studied the problems of reading x-rays and the kind of things they turned up. Their findings were a little shocking to some of the clinicians in the field, and I think that you have somewhat the same problem at the present time, for it is a problem that will always be with us in the diagnostic area.

The second major issue that occurred to me, as I read through this paper, seemed to be the question of integration—or interplay—between observations which are made on the population, and observations which are made in the laboratory and by the clinician.

I will try to indicate what I mean by writing this, shall we call it, chemical equation. The arrow indicates reversible reactions,

$$\left.\begin{array}{c}\text{Population}\\\text{Observations}\end{array}\right] \longleftrightarrow \left[\begin{array}{l}\text{Clinical and Laboratory}\\\text{Observations}\end{array}\right.$$

We have "Clinical and Laboratory Observations" on the one side, and we have "Population Observations" on the other side. If you like, we can put the sociological type of observation on the side of the population, and perhaps we might want to make it a three-way equation, but we will probably be talking more about that in some of the later papers. As the equation shows, these are interrelated-type of observations. However, I wonder whether we have really looked at the mental health problem from this standpoint of a "reversible" reaction.

Let me see if I can illustrate what I mean quickly with the example of pellagra. For example, if I remember my school days well

enough, when Goldberger and Sydenstrycker were studying pellagra, they first got the idea that it had something to do with nutrition from clinical and laboratory observations. They noticed in the clinical situation that most of these cases were poor, rural individuals. They also had certain kinds of laboratory evidence that suggested that possibly some nutritional factor was involved but this was just a hunch or hypothesis at this point.

This led them out into the population, particularly Goldberger, and here they were able to pin down the idea that something in the diet had something to do with the development of pellagra. Obviously there were social factors involved in this, also.

The interesting thing to me is that they didn't stop there. They came back into the laboratory after the population observations and began to see if they could isolate the particular factor in the diet that was involved as one of the agents in the development of pellagra. I don't remember well enough whether they actually isolated the B complex and niacin or just what they did, but I do remember that they were able to identify some elements in the diet that were responsible for the development of pellagra.

You can make this same argument for cholera, although taking it back into the laboratory and the identification of the cholera organism took place quite a bit later in time.

Now I would like to take this kind of an approach over into the mental health field and see if I can make the connection. Let us take the question of prematurity. This is a particular kind of agent which Dr. MacMahon has mentioned and which occupies a good portion of his paper.

If one were able to rank the various agents in order of importance relative to the frequency of mental disorders associated with them, I think prematurity would probably head the list.

About 6 per cent of the single births in the United States are premature. We know very little about the causes of prematurity. There is, in the literature in this field, as far as I am aware (and you, of course, are more aware of this than I), very little detailed description of the physiological and biochemical dynamics of pregnancy— what happens to the biochemical structure of this woman as she goes through pregnancy.

There seems to be very little information about the changes that take place during the course of pregnancy, and there is still less in-

formation in the literature relating the various patterns which presumably exist to the occurrence of prematurity.

This is just a long-winded way of saying what your medical student said about there being very little information available.

·As I got to thinking about this I wondered whether this is due to lack of interest among obstetricians about this, so I started to look around the members of the group here. As far as I am aware, there are no obstetricians in our group. And while I didn't take the trouble to go through a medical directory to see how many authors were obstetricians amongst all the references that you gave, I did get the general impression that there weren't a great many of them. The one outstanding individual in this area seems to be Dr. Eastman at Johns Hopkins, but he seems to be the exception rather than rule.

It was rather interesting to me that Dr. Böök had already spoken of the need for finding physical or biochemical correlates, and I again refer to the need for an interplay between these two sides of this so-called chemical equation.

I have the feeling when I read this sort of material that what has happened is that one side of this equation—the right-hand side—has been examined in more or less detail; this is the part that Dr. MacMahon has reviewed. But so far there is relatively little on the left-hand side of the equation; or if there is such information available, we haven't yet linked it up with the right-hand side.

In my concept of epidemiology, one does not have a complete epidemiological picture until one sees the relationship between the two sides of the equation. I am sometimes a little concerned to find people only meaning the right-hand side of the equation when they use the term "epidemiology." If we go back to classical epidemiology, we will find that the epidemiologists we hold up as the fathers of the discipline did not think of the term as involving only one side of this equation.

Dr. MacMahon suggests that we should develop further a large number of cohort studies in this area. Usually these studies, like those of Dr. Pasamanick and others, start with the premature baby and follow this baby forward. Relatively little seems to be known about their mothers, yet we know from the studies of Yerushalmy and others that the mothers who have premature babies or complications of pregnancy are those who have had similar difficulties in previous pregnancies. This is a fairly well demonstrated fact.

Can we make use of this observation to try to further characterize these women physiologically and biochemically?

One of the questions that occurred to me to wonder about, was the mental health history of all of the offspring of these mothers who have premature babies or who have had complications of pregnancy as compared with controls.

So far as I am aware, the usual thing that is done is to take the current pregnancy and compare it with a control. But wouldn't we add to the strength of the evidence if we took the whole picture, recognizing the fact that these mothers are somehow a selected group? Something must happen to these mothers which makes them much more likely to have a subsequent premature baby or a complication of pregnancy.

In this regard, the studies of the National Institute of Neurological Diseases and Blindness, which I imagine most of you are familiar with, should provide considerable data on the mother because, as you know, they are taking very detailed observations during the course of pregnancy on mothers who come to medical centers all over the country.

This raises another issue. I don't know what kind of an issue this is, or how one would classify this issue—whether one would call it administrative, financial or logical or what—but I will describe it to you and you can worry about its classification.

Is it only possible to obtain the kind of information we are talking about from such multimillion dollar studies as the National Institute of Neurological Diseases and Blindness study on selected populations? If that is so, then we are in an awkward kind of position. But I hardly think this is the only approach.

The NINDB study uses a shotgun approach to this problem, and perhaps this is necessary at this stage. However, I wondered in reading over Dr. MacMahon's review, whether any of the data now available, were they to be examined in the light of present biochemical and physiological knowledge, would permit the formulation of more specific hypotheses which could be tested without raising the limit on the national debt?

Is it possible to write a review, one like Dr. MacMahon's but which is concerned with the left-hand side of the equation, and then try to put both sides together, or don't we have any observations on the left-hand side of that equation?

Dr. MacMahon's review impressed me with the need for better appreciation of the requirements for research and for some uniform way of communicating results in this field.

For example, Dr. MacMahon makes the statement, "Eastman and DeLeon, in one of the few controlled studies, studied 96 children with cerebral palsy with 11,195 surviving normal children. These data would suggest an incidence of cerebral palsy 40 times higher in those who did not breathe for six minutes or more than in those who breathed within six minutes."[1]

The thing that interested me here is the notation that it was "one of the few controlled studies. . . ." As one goes through this material one finds over and over again that one is tempted to make this kind of a statement. This is disturbing to a statistician.

This lack of controls, of proper design of the experiment, is a problem common to many of these areas. What can be done about it?

While perhaps I should take a fatalistic point of view and say, "Well, as time goes on these things tend to iron themselves out," I just wonder whether there is any way of hurrying the process up.

It concerns me that in this field—which is such a difficult field anyway because of the problems of diagnosis that I mentioned earlier and the general difficulty of defining the things that one is measuring—that adequate research designs seem to be so often lacking.

The other area I want to speak of is the reporting of results. I had the experience recently of sitting in on Dr. James' Subcommittee on Primary Prevention in Mental Health of the American Public Health Association, and trying to get some notion of what the incidence rates were for the various types of mental disorders. By ranking them, the public health administrator could get some notion of what problems he might want to concentrate on first. I found it a very frustrating experience because one person would say: "Of the total number of cases of German measles, such-and-such a number of the children developed some kind of mental defect." While the next would say: "Of the cases of children with mental defects, a certain proportion of them had previously had mothers who had German measles." But one cannot put the two statements together, and as one reads through the literature it gets more and more frustrating. Lest I wind up a mental health problem myself, I quit reading it and decided to bring the problem to you, hoping that perhaps you could suggest some

[1] P. 31.

way of developing a little more uniformity into the way in which results are presented so that they can be compared.

The final thing I want to speak of takes advantage of Dr. Boudreau's suggestion that we might harp on some particular aspect which might be of specific interest to us individually. This has to do with the last section of Dr. MacMahon's paper in which he takes up the kind of population observations that have been made, such as relationship between the season of birth, certain kinds of measurements of intelligence, and so on.

One of the things Dr. MacMahon speaks of is the relationship of birth order with chronic brain syndromes that originate in the perinatal period, for example, epilepsy. There is also discussion on the influence of maternal age.

The thing that struck me as being rather interesting and curious is that some of these things are correlated with birth order but not with age, and, conversely, when birth order is held constant, some of these things vary with age of the mother.

If one holds the age of the mother constant, and one finds something varying with birth order, then something seems to happen to this woman from one pregnancy to the next. What is this thing? What is happening to this woman?

Conversely, if one holds the birth order constant and something varies with age, presumably there is some physiological correlate with the aging process—possibly this is an environmental factor that operates. But what is this thing that varies with age, yet doesn't seem to vary with birth order?

As I got to be curious it led me around in a circle to where I first started, namely, what is known about the biochemical and physiological changes in pregnant and non-pregnant females with age? And how does this relate to the kind of observation which Dr. MacMahon has made in his paper?

These are some of the thoughts that occurred to me. The only observation I really have to make is to wonder how one can fill in the equation that I set up on the blackboard.

SUMMARY OF DISCUSSION

1. Dr. Rosen expanding on Dr. Densen's remarks, asked about the changes which take place in women as they age that can affect the

course of a pregnancy. He pointed to two approaches which have not been pursued in great detail.

One approach is to ask, What actually happens in the placenta and in placentation in the older woman? The role of placentation might well be a point of departure for future studies. The other approach is to study the relation of parity to the immunochemistry of the mother. For example, are antibodies produced increasingly as the number of pregnancies increases and, if so, which ones? While this question has been studied it has not been studied specifically in relation to parity. These are two areas where research might prove to be useful.

However, when an association is found between parity and some condition of the offspring, it is necessary to interpret it with caution. There seems little doubt that some of these parity associations result from physiologic changes in the woman, yet it should not be assumed that something necessarily happened to change the same woman from one pregnancy to the next. Because, in the aggregate, the class of women having their first child, and the class of women having their sixth child, are composed of two quite different kinds of women. Undoubtedly selectivity is at work. There are characteristics that tend to place women at different levels of parity; and it might be that it was some of these characteristics rather than parity itself that brought about an observed association with some condition in the offspring.

2. Dr. Pasamanick asserted that it was not enough to give attention to each factor as a separate variable. More reference was needed to the interaction among variables. As an instance, when Dr. MacMahon discussed natal events he ignored to some extent the interrelationship of these with prenatal events.

Thus natal difficulties such as apnea and cyanosis in the infant showed a very high association with complications of pregnancy. It might very well be that prenatal damage in the brain respiratory centers of the fetus accounted for natal respiratory difficulties. In fact, there was evidence from pathological examinations which showed that it was either the premature infant or the infant who was subjected to some complication of pregnancy, who was chiefly affected by anoxic damage.

3. Another interrelationship that he mentioned was the high inverse association of socio-economic status with complications of preg-

nancy and prematurity. This relationship was worth examining for two reasons. It might provide clues to etiology, and it was undoubtedly complicating and confounding the import of many social and cultural variables.

A number of specific comments were offered by Dr. Pasamanick that stemmed from the studies that he and his associates had done.

4. Very little relationship was found between obstetric complications and neuropsychiatric disorders in the offspring. But this investigation, like others of its kind, was done in cities where obstetrical care was relatively good. Perhaps elsewhere difficulties in labor and surgical procedures might be found to play a more important role; although the evidence for suspecting it was not strong.

5. Some of the reservations expressed by Dr. MacMahon about the methodolgy used in a number of Dr. Pasamanick's studies on the complications of pregnancy were well taken. However, Dr. Mac-Mahon's point about bias with regard to socio-economic status in the experimental and control samples (pp. 44–45) needed clarification: Bias might operate either for or against the hypothesis under test, though perhaps more heavily against it. The reasoning was that if those who were socio-economically retarded were removed from the experimental group, the differences between cases and controls would be even greater. Possible evidence for this supposition was derived by analyzing the dependent variables by I.Q. in the Negro group.

6. As to the question of socio-economic differences in the distribution of births by season, there existed very definite evidence based upon data covering five years of births in Baltimore. The seasonal distribution of births in the upper economic groups showed extremely little variation, while the lower economic groups, both Negro and white, showed a large decrease in births during the winter. This finding was important to any hypothesis that related seasonal variation in the birth of mental defectives to seasonal variation in the over-all birth rate: it would seem necessary to control for social class to avoid bias.

7. On the basis of all births in the United States during 1955, it was found that there was a significantly lower birth weight in summertime. This fact may be attributed, in accord with an entire chain of evidence, to decreased nutritional intake in summertime, considering that the fetus takes on weight largely in the last trimester.

8. No relationship at all was found between the births of mentally defective children and the 1918–1919 'flu epidemic. This finding was not discussed in Dr. Pasamanick's paper on seasonal variation, although the possibility of such a relationship was the original reason for taking it up later. Possibly, if the finding had been made known, the subsequent studies on Asian 'flu might not have been considered necessary. In any case, it seems a fact that 'flu does not have any prenatal effect.

9. On the relationship of season of birth to schizophrenia, most studies in the literature reported that more schizophrenics were born in wintertime. But this finding was not confirmed by a study of all admissions to the Columbus State Hospital over a sixty-year period.

10. However, temperature variation (which had been found related to mental retardation) *was* found related to schizophrenia. There was a very significantly higher rate of schizophrenia in individuals born after hot summers than after cool summers. At present, the only hypothesis that was advanced was that a hot summer might produce enough prenatal damage to act as a precipitating factor.

DR. MACMAHON: It is important to distinguish two general types of explanation of associations of fetal characteristics with birth order. The first, and more obvious, relates to maternal physiologic or pathologic changes that proceed in association with childbirth. Associations having explanations of this type would be apparent in comparisons of the same mothers at different birth orders. The second type of explanation derives from the fact that in a cross section of births in a population, different social, ethnic and other cultural classes are represented in differing proportions in the various maternal age and parity groups. It seems likely that both these types of explanation are pertinent to birth order associations in the mental disorders; having noted a birth order association, we cannot jump to one conclusion or the other.

Dr. Pasamanick's point (Point 2) concerning the identification of causative complexes as distinct from single variables is an important and difficult one. Certainly, although epidemiologic research generally proceeds by the identification of one or two factors at a time, preventive measures frequently involve alteration of broad complexes such as "cleanliness" of food and water, or "quality" of obstetric care.

As stated in our review, we have been unable to find convincing evidence of prenatal influence in the psychoses or neuroses. Dr. Pasamanick's observation of the effect of temperature during intra-uterine life on incidence of schizophrenia is therefore particularly interesting (Point 10). It seems strange, however, that temperature variations of the order noted for the same season between years could have an influence, while variation between seasons within years does not.