

EDITORIAL

Epilepsy: some epidemiological aspects¹

The epilepsies have been subject to effective chemical control for a good half century longer than the functional psychoses. Phenobarbitone, which was preceded by over 50 years by bromides, came into use in 1913, dilantin in 1938. Perhaps this early advent of successful pharmacological control of the epilepsies, as compared with that of the functional psychoses, damped epidemiological research into the subject. We venture that there is less epidemiological knowledge about the distribution and aetiology of the epilepsies than about the psychoses. This neglect of the epidemiology of seizure disorders has left fallow a most intriguing psychiatric issue, namely, the association of temporal lobe epilepsy with psychiatric disorders, and with schizophrenia in particular. We shall concern ourselves here with the more general epidemiological background of the epilepsies.

Anticonvulsants permit the control of seizures in 60–80 % of epileptic patients (Rodin, 1972). After a 20-year follow-up, some 70 % of patients have been found free of seizures for 5 years (Anneegers *et al.* 1979). Still, as a recent review in this journal suggested, long-term use of anticonvulsants may produce mental deterioration (Trimble & Reynolds, 1976). Experiments on preweanling and postweanling rats also suggest, alarmingly, that phenobarbitone given during the brain growth spurt, or even during the subsequent deceleration, retards brain growth and disturbs behaviour (Diaz *et al.* 1977; Diaz & Schain, 1977). In addition, many persons with seizures go undiagnosed and untreated or improperly medicated. A recent report has drawn attention to under-medication and over-medication that is widespread and substantial in certain institutionalized settings (Murphy & D'Souza, 1977). Primary prevention is surely what we must aim for in the long run – an aim which can only be achieved by a search for causes. This goal is ambitious. At present, about 70 % of seizures identified in population surveys are ascribed to unknown causes (Hauser, 1978). Even this figure is an underestimate, since the environmental and genetic 'causes' often cited are best treated as hypothetical rather than established.

The search for causes begins with a quest for variations in the frequency of the disorder. Since 1950, at least 36 surveys – whether concerned exclusively with seizure disorders in particular or with neurological disorders in general – have been conducted in various settings around the world (see bibliography). Fourteen of these deal exclusively with infants and children. Worldwide, the reported incidence rates of the epilepsies for all ages combined range from 0.173 per 1000 in Niigata City, Japan (Sato, 1964) to 1 per 1000 in Australia (Crombie *et al.* 1960). Within England itself, the reported rates vary from 0.30 per 1000 in Carlisle (Brewis *et al.* 1966) to 0.73 per 1000 in 14 general practices in southeast England (Pond *et al.* 1960). Prevalence rates for all ages combined range from 1.50 per 1000, again in Niigata City, Japan (Sato, 1964), to 20 per 1000 among the Wapogoro tribe in Tanzania (Jilek & Jilek-Aall, 1970). In England, prevalence rates have varied from 3.33 (Logan & Cushion, 1958) to 7.90 per 1000 (Pond *et al.* 1960).

For many conditions true variation of this order is not beyond the limits of credibility, but the data to hand for the epilepsies conflate the contributions of research methods and those of morbidity. Studies employ non-comparable definitions, a variety of ways of finding and ascertaining cases, and different measures of frequency. At one extreme, Hauser & Kurland (1975) restrict epilepsy to recurrent seizures occurring in the absence of identifiable cause. At the other extreme, Gudmundsson (1966) includes isolated afebrile seizures, and Pond *et al.* (1960) include febrile seizures as well. Inclusion of isolated and/or febrile seizures can inflate estimates of incidence or prevalence anywhere from 1.7 (Hauser & Kurland, 1975) to 37 times (Lessell *et al.* 1962). Most surveys rely on medical

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records for case finding, a practice which inevitably results in under-estimation. The potential magnitude of such errors is suggested by an Eastern European and by an Israeli study. In Warsaw, 27 % of epileptic persons identified by means of a general population survey were unknown as seizure cases in medical records (Zielinsky, 1974*a*). In Beer-Sheva, Israel, a study of seizures among children in the first 5 years of life reported that 48 % of the cases had never been previously brought to the attention of medical personnel (Costeff, 1965).

Frequency measures of the epilepsies are different from those obtained with apparently comparable developmental disorders. For instance, with mental retardation, often an associated developmental disorder, incidence is difficult to measure and even to grasp conceptually (Stein & Susser, 1974). The expression of retarded mental growth must await the subtle unfolding of psychological and social development. On the other hand, the prevalence of mental retardation at a given age or point in time is readily determined; the classifying and labelling process so central to the educational systems of all developed societies yields both the numerator of the rate and a constantly enumerated, captive population as denominator. In contrast, the frank and usually explosive onset of the epilepsies poses fewer difficulties for the satisfactory measurement of incidence. With the epilepsies, it is the determination of prevalence that is more problematic. In industrial societies a large proportion of cases is adequately controlled by medication. Does a patient on anticonvulsants, who has been seizure free for 5 years, constitute a case? Shall we say 'once an epileptic, always an epileptic' (Kurtzke, 1972)? These questions are of pressing concern, not only in the context of frequency measures, but because of the social stigma and negative self-concept carried by the diagnosis of epilepsy.

We turn now to consider the variations in incidence and prevalence that exist in the literature. There is probably some excess of the epilepsies among males. Among incidence studies reporting rates for the epilepsies at all ages, only 7 provide usable sex ratios. The ratio is virtual unity in 1 (Juil-Jensen & Ipsen, 1975); males are in slight excess in 4 (Crombie *et al.* 1960; Sato, 1964; deGraaf, 1974; Hauser & Kurland, 1975); and in modest excess in another (Gudmundsson, 1966). In the remaining study the rate among females was somewhat higher than that among males (Pond *et al.* 1960). The 3 incidence studies reporting rates specifically for recurrent afebrile seizures all show higher rates for males.

Among 15 prevalence studies that report rates by sex for all ages combined, the ratios in 11 reflect a generally slight excess for males (Logan & Cushion, 1958; Crombie *et al.* 1960; Lessell *et al.* 1962; Sato, 1964; Gudmundsson, 1966; Wajsbort *et al.* 1967; Leibowitz & Alter, 1968; Mathai *et al.* 1968; Levy, 1970; Zielinski, 1974*b*; Hauser & Kurland, 1975); in 2, a slight excess for females (Pond *et al.* 1960; Juil-Jensen & Ipsen, 1975); and in another 2 they approach unity (Brewis *et al.* 1966; deGraaf, 1974). Eight studies give prevalence rates separately for recurrent afebrile seizures. Six of these report higher rates for males; 2, equal rates. None of the 15 studies finds a substantial difference in rates.

The higher prevalence rate among males may result from higher incidence, less successful seizure management, or greater duration of the disorder among males, or all three. Further, these studies may reflect differential help-seeking behaviour as much as seizure morbidity. The majority generated their data exclusively from medical records rather than from general population surveys. Because of the minor or negligible differences in the sex ratios of incidence studies, and the non-causal factors which contribute to the differences in the sex ratios of prevalence studies, strong aetiological hypotheses do not emerge from these studies.

Eight studies addressed the issue of the social class distribution of the epilepsies. Their conclusions are widely different and sometimes internally contradictory. One might anticipate that seizure disorders would be inversely related to social class because of so-called 'downward drift'. This model of social mobility would predict an accumulation of seizure cases at the bottom of the social order. Like other chronic disorders, seizures are bound to interfere, in varying degrees, with social and economic functioning. If inadequate prenatal, perinatal or postnatal care plays a role in the aetiology of seizures, that would lead to a similar prediction.

The prediction is supported by the prevalence survey of 67 general practices in England and Wales

conducted by Crombie *et al.* (1960) in the late 1950s, and also by the more detailed survey of 14 of these practices by Pond *et al.* (1960). In these overlapping data, both groups of investigators report an impression of an inverse relationship between the frequency of seizure disorders and social class.

Rather different associations emerge from a Scandinavian survey and from another conducted several years earlier in England. Gudmundsson's data (1966) point to a curvilinear relationship between social class and the prevalence of the epilepsies in Iceland. Rates were higher in the middle class and lower at each end of the social spectrum. Gudmundsson dismissed these findings as unrelated to an aetiological factor. He explained the higher rates in the middle class as an artefact of the manner in which he obtained a denominator for this rate, and the lower rates in the upper class as a product of downward drift. The 1950s survey of 106 general practices in England by Logan & Cushion (Logan & Cushion, 1958; Logan, 1962) has often been cited as demonstrating an inverse relationship between social class and the epilepsies. In fact, to the extent that any relation is discernible in the data, it is curvilinear, but in a reverse direction from that reported by Gudmundsson.

The prevalence studies of seizure disorders for all ages combined discussed above do not present findings for specific seizure subtypes by social class. For such analyses we must turn to studies of birth cohorts, most of them followed into middle childhood. Their results afford a complex and provocative picture. In these studies, the social class of the cohort is derived from parental attributes recorded before the child's birth, and they are less vulnerable to artefacts of misclassification posed by phenomena such as downward drift.

In the Newcastle-upon-Tyne 1947 '1000 family' cohort, the incidence rate in the first 5 years of life among surviving children was higher the lower the class for all seizure types, except for those associated with infective illnesses such as gastro-enteritis, rubella and meningitis (Miller *et al.* 1960). The incidence rate also increased with increasing deficiency in the physical care parents gave their children. The results from the 1946 British national cohort of some 5000 children are at first sight paradoxical. In this cohort, children from higher social classes had experienced idiopathic seizures more frequently in the first 2 years of life than children from the lower classes. When homes were rated on the basis of standards of parental care and interest rather than by occupational class, however, lower standards of care were associated with higher rates of idiopathic seizures – a finding which parallels that of the Newcastle study. Also, as in the Newcastle cohort, the distribution of seizures arising from evident precipitating causes or illnesses was unrelated either to social class or to standards of care. Paradoxes are added by 2 other cohort studies: the Collaborative Perinatal Project in the United States (1959–63), which comprised more than 50000 births; and the 1958 British National Child Development Study about 17000 births. Preliminary analyses for the first year of life in the United States cohort (Myriantopoulos, 1972), and in the first 11 years in the British cohort (Ross, 1973), failed to uncover straightforward or discernible associations between social class and the incidence of either febrile or afebrile seizures.

Those social class differences that do emerge from these studies could reflect true variation in the frequency of the epilepsies among groups enjoying widely different levels of health care, nutrition, and hygiene. Ascertainment biases constitute a serious potential source of error in these investigations, however, since so much depends on the responses of parents to illness. Whether they perceive infant convulsions as illness, the degree of alarm that attends such perceptions, and their propensity to call on medical services for help in such circumstances, may all vary with social class and all may colour their reports on interview.

There has been interest in cross-cultural research on the epilepsies for many years. Epidemiological surveys of varying quality exist for a number of ethnic and racial groups. A review of ethnic variations, however, soon runs up against the decisive influence of study methods on reported rates. For this reason, legitimate ethnic and racial comparisons can only be made within studies.

In a literature search on racial variation in the epilepsies, Rodin (1972) failed to locate any studies reporting rates for more than one race or ethnic group. As a second best strategy for addressing this research question, he calculated the mean prevalence of seizure disorders reported in 10 North American and European studies (4.5 per 1000) and compared this with the mean based upon 10

African studies (4.4 per 1000). This apparent convergence of rates cannot simply be dismissed, but it is a brave assumption that broad and narrow definitions of epilepsy are equally distributed across the African, North American and European research projects, and that the communities surveyed on these continents were randomly selected or representative.

Results from the Columbia University sector of the Collaborative Perinatal Project suggest that ethnic differences in the frequency of seizure disorders may, in fact, exist. In this cohort, comprised of approximately 625 White, 850 Black and 600 Puerto Rican children, the incidence rate, in the first 7 or 8 years of life both for febrile and afebrile seizures, was much the highest among Puerto Rican children. The incidence rate of febrile seizures among Whites exceeded that for Blacks, whereas for afebrile seizures the reverse was true (Gates, 1972). While one of these findings may be an ascertainment phenomenon, the other cannot be accounted for by the same logic.

A different picture emerges from the entire US Collaborative Perinatal Project data for incidence among Blacks and Whites in the first year of life. Among infants of all birth weights taken together, the total incidence of seizures did not differ between Blacks and Whites. Among low birth weight infants of less than 2500 g, however, the rate of afebrile seizures among Blacks was about twice as high as that among Whites, and of febrile seizures about 20 % higher (Myriantopoulos, 1972). No test was performed to show whether these differences were independent of social class. These preliminary findings, which involve relatively small numbers, must be treated with caution.

Two other projects in the United States, the first in Washington County, Maryland (Rose *et al.* 1973), the second in Multnomah County, Oregon (Meighan *et al.* 1976), raise further intriguing questions about the possibility of true ethnic or geographic variations in the frequency of seizure disorders. These studies, although undertaken by separate teams, utilized nearly identical case finding methods involving mailed questionnaires. In Maryland the overall rate for all types of seizures in 1900 3rd grade children was 18.6 per 1000; in Oregon among 5300 3rd graders the rate was 9.7. Such a two-fold difference deserves further scrutiny and replication of the study design at other sites. Although neither group of investigators specified the exact ethnic composition of the target populations, US census data for Multnomah County (US Dept. of Commerce, 1973) and statistics supplied by Rose *et al.* (1973) indicate that the general population of both counties was over 95 % White.

The pattern of age-specific incidence rates, reported by many surveys, provides one consistent vein among the many inconsistencies to which we have alluded (Crombie *et al.* 1960; Brewis *et al.* 1966; Mathai *et al.* 1968; deGraaf, 1974; Hauser & Kurland, 1975; Juul-Jensen & Ipsen, 1975). Rates are highest among neonates, decline steadily until the end of the second decade, and then level off or continue to decline more gradually for the remainder of the life span. The Rochester, Minnesota, study of Hauser & Kurland (1975) is unique in showing an upswing in later life, starting approximately at age 60. Although an increased incidence with advancing age might be expected, given the link between age and organic cerebral disorder, this curvilinear relationship with age remains to be replicated elsewhere. Bea van den Berg and the late Jacob Yerushalmy, using a 1960–7 cohort of 18 500 births in Oakland, California, report to date the most refined age-specific incidence rates for infants and children. Afebrile seizures occurred in 0.76 per 1000 neonates, then in the second month of life dropped to less than half that rate, 0.33 per 1000. The rate for the remainder of the first year stabilized at a monthly rate of about 0.20 per 1000 and continued to decline unevenly thereafter. By the age of 5, about 10 per 1000 of the cohort had had at least one afebrile fit (Van den Berg & Yerushalmy, 1969).

With regard to the absolute values of the age-specific rates that comprise this regular pattern, however, we find the familiar wide range of variation. Only by the age of 10 did the Rochester, Minnesota, rates reach the cumulative incidence for isolated and recurrent seizures of 10 per 1000 reached by age 5 in Oakland (Hauser & Kurland, 1975). Other incidence rates, including those from 2 British studies which include all types of fits of whatever origin, are much higher than either of these: an estimated 25 per 1000 in the first 2 years of life in the 1946 British national birth cohort (Cooper, 1965), approximately 61 per 1000 in the first 5 years in the Newcastle-upon-Tyne 1000 family study (Miller *et al.* 1960), and an extraordinary cumulative rate of 192 per 1000 to age 5 in an Israeli study

(Costeff, 1965). From the data at hand, we are free to choose between true variation, under-reporting with many false negatives, over-reporting with many false positives, or all three.

Nonetheless, all studies agree upon the high rates of afebrile seizures in the early months and years of life. Many afebrile seizures may represent failures of inhibitory mechanisms in the immature brain. It is plausible to view these failures as caused by specific prenatal, perinatal or early postnatal factors. Several kinds of evidence support this view. Studies of extensive clinical series have implicated a wide variety of prenatal and perinatal factors in the causes of seizures appearing in early life. These investigators are usually limited to causal inferences drawn from internal comparisons among cases or from implicit comparisons with general population rates. Among prenatal conditions, maternal bleeding, infections and toxæmia are suspected of causal involvement in the early epilepsies. Prematurity, prolonged labour, forceps delivery, neonatal hypoxia and low birthweight have all been mentioned as possible peripartum aetiological factors (Ounsted *et al.* 1966; Lier & Zachau-Christiansen, 1970; Bergamini *et al.* 1977; Chevrie & Aicardi, 1977). Two intensive, controlled studies have demonstrated associations between transient metabolic disturbances, such as hypocalcaemia and hypoglycaemia, and neonatal seizures (Brown *et al.* 1972; Keen & Lee, 1973).

If these factors are at work, it is a reasonable hope that advances in obstetrics and neonatology would be reflected in a reduced incidence of seizures, especially those of early onset. And indeed, this hope appears to be realized in the Rochester, Minnesota, data. For the period 1965–74, as compared with the 2 preceding decades, these data suggest that there was a decline in the incidence of recurrent seizures in infants under age 1 (Annegers *et al.* 1977). This reduced incidence could be the result of changing childbearing patterns or even of the better management of single seizure patients. More likely, it is a genuine consequence of the interruption by improved medical care of the causal pathways between noxious prenatal or perinatal factors and subsequent infantile seizures.

The possible role of prenatal and perinatal factors in the epilepsies has been explored in 2 case control studies in the USA in the 1950s and 1960s. Lilienfeld & Pasamanick (1954) compared the perinatal and prenatal records of 564 epileptic children with the records of matched controls selected, from birth registers. Among the epileptic children they found an excess of complications of pregnancy and delivery, and of abnormal neonatal conditions such as cyanosis. The findings among Blacks were similar to those among Whites, but the differences between Black cases and controls were not statistically significant. Henderson *et al.* (1964) replicated this study using a larger sample to test the findings among Blacks specifically, but also failed to find statistically significant associations between epilepsy and various prenatal and perinatal factors.

These hypotheses need further testing. There are 2 obvious weaknesses in these enterprising early controlled studies: first, an unavoidable crudeness in the prenatal and perinatal independent variables, and secondly a similar lack of precision in the dependent variable, the diagnosis of epilepsy. Advances in the years intervening since those studies permit refinement in both the independent and dependent variables, and thus an enhanced power to detect an effect. Neonatal care has become greatly sophisticated in the past decade, and data can be compiled on the physiological state of the infant, for instance in terms of blood sugar, electrolytes, body temperature and infant behaviour. Even the simple Apgar score was not available to the earlier studies. On the diagnostic side, the changes are no less dramatic, although they involve classification more than technology.

The prospects for precision in the matter of classification have been greatly improved by the recent emphasis on the clinical phenomenology of seizures, an approach reflected in the classification adopted in 1970 by the International League Against Epilepsy (Gastaut, 1970). One consequence of this new classification has been the greater recognition of seizures with focal or partial onset. The Lilienfeld & Pasamanick work of the 1950s, for example, confined its seizure types to grand mal, petit mal, 'other' and combinations of the three (Pasamanick & Lilienfeld, 1954). Focal seizures were not discussed explicitly, although abnormal EEG recordings with localization were distinguished in 27 % of available materials. In Hauser & Kurland's paper of 1975, which relied on the new classification, seizures of focal origin constituted more than 60 % of all recurrent seizure types. This dramatic shift is essentially the result of a revised nosology. The Rochester, Minnesota, data used

by Hauser & Kurland extended through the 3 decades beginning in 1935. What changed were not the data, but the use made of them. Focal seizures, it must be added, are those most likely to be the consequence of perinatal factors.

In the current classification offered by the International League Against Epilepsy, seizures of focal origin are termed partial seizures, and described as having either elementary or complex symptomatology. In prior classifications, partial seizures with complex symptomatology were referred to as 'psychomotor' or 'temporal lobe' seizures. In the Rochester, Minnesota, study these constituted at least 40% of partial seizures and more than 25% of all recurrent seizures generally (Hauser & Kurland, 1975). These seizures are particularly resistant to medication and comprise the group in which surgery is resorted to most often. The possibility of primary prevention of this seizure type deserves further study.¹

In 1953 Earle, Baldwin and Penfield (Earle *et al.* 1953) put forward a hypothesis which linked temporal lobe epilepsy with birth trauma. The mesial temporal sclerosis they had observed in the excised brains of temporal lobe epileptics, they suggested, was the consequence of herniation of the temporal lobe through the incisura of the tentorium, produced by mechanical compression of the head at birth. Falconer *et al.* (1964), noting high frequency of febrile convulsions in the histories of persons coming to surgery with intractable temporal lobe epilepsy, and Ounsted *et al.* (1966), observing a similar history in their series of temporal lobe epileptics, have argued the alternative hypothesis that the mesial sclerosis results from anoxia and cerebral oedema produced by prolonged febrile convulsions in childhood.

We know of no published study which has made an unbiased test of the association of temporal lobe epilepsy with febrile convulsions. P. West, E. M. Ross and N. R. Butler (personal communication), in a careful unpublished analysis of the 1958 British national birth cohort, have not found an association of febrile convulsions with temporal lobe epilepsy. This result emphasizes the fierce bias that can arise from the study among hospital cases alone of associations between different disorders.

While a specific association of childhood febrile seizures with temporal lobe epilepsy remains to be established, there is little doubt that early febrile seizures are associated with an excess risk of subsequent recurrent afebrile seizures generally (Van den Berg & Yerushalmy, 1969; Hauser & Kurland, 1975; Nelson & Ellenberg, 1976). The aetiological question is whether febrile seizures 'kindle' later seizures, whether they indicate an epileptic predisposition, or whether both processes are involved. The intriguing kindling hypothesis provides one justification for the current prophylactic use of anti-convulsants in treating children who have experienced febrile seizures. Although several controlled trials have demonstrated that phenobarbital can reduce the recurrence of febrile seizures (Faerø *et al.* 1972; Wallace, 1975; Wolf *et al.* 1977), the larger question of the contribution of febrile seizures to subsequent afebrile seizures remains unanswered. For the present, the hypothesis rests on the demonstration of kindling in animal experimental studies, and on suggestive data on the evolution of epilepsy after head injury (Jennett, 1965).

Predisposition is almost certainly a factor in the association of febrile and afebrile seizures. A familial history of febrile seizures has been found in association with certain recurrent afebrile seizure types (Ounsted *et al.* 1966; Hauser & Kurland, 1975; Tsuboi & Endo, 1977). Recurrent afebrile seizures too have been found to have a familial distribution (Kimball & Hersh, 1954; Metrakos & Metrakos, 1961; Tsuboi & Christian, 1973). Among these reports, variation and conflict about familial distributions is hardly less than about the frequencies described above. Undoubtedly, every individual has a threshold above which an appropriate stimulus will produce a seizure. A rigorous effort by Anderson (1978) has brought a degree of order out of chaos. In his review, he took care to specify the type of seizure, and also to distinguish between seizures and electro-encephalographic patterns.

¹ Temporal lobe seizures are also of special interest to psychiatry because of the suspected link between temporal lobe epilepsy and 'functional' psychoses. This research area has wide implications for the biological bases of functional psychiatric disorders, and deserves review in its own right. We would contend that few investigators have employed appropriate study designs or samples of sufficient size to which to address their hypotheses.

The most provocative result comes from the Rochester, Minnesota, studies. Three decades of accessible records in a single community enabled the research team to follow the offspring of the probands. Annegers *et al.* (1976) found an excess of recurrent afebrile seizures in offspring of 183 epileptic mothers, but none among the offspring of 108 epileptic fathers. (This excess was particularly striking for mothers with seizures of focal, as compared with generalized, onset.) The finding is probably not aberrant. Close examination of other family studies reveals a similar bias towards maternal transmission (Tsuboi & Christian, 1973; Gerken *et al.* 1977; Tsuboi & Endo, 1977). In these studies, the possibility of an artefact cannot be excluded, since a history of epilepsy in mothers is almost always easier to obtain than in fathers. The Rochester cohort study averts this difficulty.

Genetic hypotheses could explain this maternal bias with a modest degree of contortion. Thus, the Rochester team cites Carter's suggestion that, in diseases which affect males more frequently than females, transmission is likely to be biased towards females, since females presumably have a higher threshold and require a heavier dose of genes to produce the given disease (Carter, 1969). Thus, females would transmit a heavier dose than males. Other hypotheses are simpler and more appealing. Maternal transmission might be induced by exposure to the intra-uterine environment, or the cytoplasm might be the vehicle (Fine, 1977). Mitochondria could be the maternal cytoplasmic carriers, since certain animal spermatozoa do not carry mitochondria and in all probability they are not carried in human sperm.

From this brief conspectus of variation in the epilepsies, we do not hesitate to make one contention. It is time for epidemiologists, epileptologists and other interested parties to set their sights on causal factors, and to begin to gather and to generate testable causal hypotheses. In the United States, this effort has been stimulated recently by publication of the *Plan for Nationwide Action on Epilepsy* (1978), a report by the Commission for the Control of Epilepsy and Its Consequences. While drawing public attention to the medical and social problems of epileptics and suggesting remedial policies, the report also summarizes present knowledge about frequency and aetiology. The Commission's work should contribute new energy and impetus to epidemiological research on aetiology.

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