MEDICAL PRACTICE

Clinical Problems

The Geography of Neurology*

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Medical geography, although an ancient form of our art, cannot be said to have really fulfilled its early promise. Although striking geographical variations have been disclosed in the incidence of many diseases—for example, in the case of gastric carcinoma—we seem to be no nearer causation. In the eighteenth and nineteenth centuries there were many accounts of the afflictions encountered in particular regions or countries, and some of them contained the first major description of a disease. Hillary's published observations in Barbados¹ include a vivid account of tropical sprue, Casal y Julian gave a description of pellagra in the Asturias,² Ratty described relapsing fever in Dublin,³ and Winterbottom described sleeping sickness (African trypanosomiasis) in Sierra Leone.⁴

Hirsch's classic *Handbook of Historical and Geographical Pathology*⁵ would probably have had more impact if the era of bacteriology had not so quickly dawned. Medical geography seemed unimportant at a time when nearly every year a new organism was identified as a cause of some human disease. Sigerist⁶ believed that medicogeographical studies became somewhat discredited because "previous work had in many ways been too ambitious, attempting a synthesis before the materials were available."

Nevertheless, comparative studies of diseases in different ethnic, national, and social groups might be expected to help in three ways. Firstly, by identifying communities which show a major difference in the frequency of a disease of unknown causation, such as multiple sclerosis, some light may be cast on aetiology. Secondly, the value of a hypothesis about the cause of a disease may be tested by examining the incidence of the disease in communities which are exposed to the suspected

factor to different degrees, as in the possible relation of congenital malformations of the nervous system to natural radiation. Thirdly, it may help to unravel the relative effects of heredity and environment by studying the frequency of a disease in two races living in the same environment or in each race separately under different conditions—Parkinson's disease and cerebrovascular accidents among white and Negro populations of the U.S.A. and Africa, for example.

The limitations of statistical studies of this kind are engendered by such factors as the difficulties in determining true prevalence and incidence rates, in comparing mortality rates, and in drawing trustworthy deductions. These methods are fraught with danger; they may never constitute final proof of a cause-and-effect relationship in a given disease, but they have already provided information of an intriguing character in several diseases.

In the realm of neurology we know that multiple sclerosis, tabes dorsalis, and vitamin B₁₂ neuropathy are rare in the tropics, but we know not why. What more can be said about the geography of neurology? Kuru is unknown beyond New Guinea. Guam is the only focus of high incidence of amyotrophic lateral sclerosis and the Parkinsonism-dementia syndrome. In Jamaica, Nigeria, Senegal, and South India paraplegias of unknown aetiology dominate the clinical scene in neurology.

In the account which follows I have chosen some neurological topics which arose during foreign visits and which illustrate this theme.

Congenital Malformations of the Nervous System

Two examples of anterior (frontoethmoidal) encephalocele in a ward round in a Bangkok hospital some years ago seemed exceptional. I had never previously seen one of these lesions, but in Bangkok they were well recognized in infants and children and they even appeared to be more common than spina bifida aperta. In the West the ratio of spina bifida aperta to cranium bifidum is about 6:1 or 7:1.⁷ In South Wales the ratio of spinal to cranial dysraphic lesions is 14:1⁸—there were 425 cases in the

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years 1956-62, 28 cranial and 397 spinal malformations. Suwanwela and Hongsaprabhas,¹⁰ in their Bangkok Hospital, saw 25 cases of anterior encephalocele in three years, during which there were only 10 spinal and three occipital meningoceles. Suwanwela¹¹ has now seen 72 cases in Bangkok. He believes that there is an unusually high incidence of anterior encephaloceles in South-east Asia, including Thailand, Malaysia, and Indonesia. It is rare in the West, Japan, China, and South India. Blood group and chromosome studies showed no unusual deviation. In a survey in northern Thailand nine cases of anterior encephalocele were found in a population of 31,582—that is, about 1 per 3,500.¹²

Penrose¹³ commented that on the whole the incidence of anencephaly is greater in Europe than in Asia and Africa. Some examples of the incidence of the three major malformations of the nervous system—anencephaly, hydrocephalus, and spina bifida—in different countries are given in the Table. The highest incidence is reported from India; the United Kingdom comes next. Japan has a significantly lower incidence of spina bifida and hydrocephalus. In Uganda the incidence of anencephaly and spina bifida was nil in 2,068 births, and there were only two cases of hydrocephalus. Simpkins and Lowe¹⁴ pointed out that in 2,000 births in the U.K. one would expect from three to eight cases of spina bifida and from three to 12 cases of anencephaly.

There may also be regional differences within the African continent. For example, during 1956-66 Odeku,¹⁵ in Nigeria, saw 97 infants with spina bifida aperta and 36 with cranium bifidum.

Congenital Malformations of the Nervous System. Incidence per 1,000 Births

	India ^{10*}	U.K. ^{11*}	U.S.A. ^{11†}	Japan ^{11‡}	Uganda ¹⁴
Births analysed	5,376	56,760	55,156	64,570	2,068
Anencephaly	4.0	1.96	0.53	0.63	0
Spina bifida	5.0	2.80	0.71	0.26	0
Hydrocephalus	3.0	1.76	0.96	0.32	1.5
Encephalocele	?	?	?	?	0

Not only does there appear to be appreciable variation from one country to another in the overall incidence of these malformations but there are also differences in the relative frequency of the different types. The ratio of encephalocele to spina bifida aperta varies—in the United Kingdom it is 1:5,^{16 17} in the U.S.A. 1:6 or 7,^{7 18 19} and in Nigeria 1:3.¹⁵ In the West occipital encephaloceles are very much commoner than anterior encephaloceles—72% occipital and 15% anterior.¹⁹

Tandon,²⁰⁻²² commenting on the high incidence of anterior encephaloceles in Lucknow and Delhi, mentioned that it is rare in other centres in India and quoted Ramamurthi, of Madras, who saw only three cases in 20 years. Tandon found that most anterior encephaloceles are isolated malformations and do not preclude normal mental and physical development. Good cosmetic and neurosurgical results may be achieved by operation when the infants are 6 to 8 weeks of age.

Nothing is known of the cause of these anterior encephaloceles. Tandon says that malnutrition may be a factor. Flatz and Sukthomya,¹² recalling the experimental evidence that vitamin deficiencies play a part in the pathogenesis of cranial soft tissue and bone defects, in particular cleft lip and palate, also say that malnutrition may have a role, although it is unlikely to be the only cause.

It would certainly be unwise to assume that some obscure racial factor were responsible for these observations.

Subarachnoid Haemorrhage

Again in Bangkok my curiosity was roused when I learnt that out of three cases of acute primary subarachnoid haemorrhage two were due to angioma and one to aneurysm. It was no coincidence. I was informed that angiomas were more commonly

found than aneurysms. No figures were available but subsequent inquiries in other Bangkok centres and in Malaya tended to confirm this evidence. Chitanondh²³ thought that the ratio was about four angiomas to one aneurysm. Selby,²⁴ after seven years at the neurosurgical unit in Kuala Lumpur, reports that "arteriovenous malformations outnumbered the aneurysms 10 to 1. Approximately two-thirds of these lesions had bled. They tended to first manifest themselves between the ages of 10 and 30 years." Inquiries in Indian neurological centres did not disclose such a high proportion of angiomas, but in most centres subarachnoid haemorrhage appeared to be less common than in the West and angiomas were more frequently diagnosed.

Ramamurthi,^{25 26} from the neurosurgical centre in Madras, reported on the rarity of bleeding aneurysms in India. Between 1958 and 1969 there were only 39 cases of acute subarachnoid haemorrhage; 20 were due to aneurysms and 19 to angiomas. From his neurosurgical department in Bombay, Dastur²⁷ reported that in the 13 years 1957-70 cerebral angiography in 89 patients, nearly all with subarachnoid haemorrhage, showed an aneurysm in 33 and an angioma in 36; in 20 the angiogram was normal. Only a few of these 89 cases presented with focal signs without haemorrhage. Over the same period there were 42 admissions because of primary intracerebral haemorrhage.

In Thailand Suwanwela *et al.*²⁸ reported that in 54 cases of primary subarachnoid haemorrhage 20 were due to aneurysm, 14 to arteriovenous malformations, and in the remaining 20 the cause was not determined.

In Singapore the ratio of arteriovenous malformation to aneurysm in subarachnoid haemorrhage is 4:1.^{29 30} An analysis of 50 cases of intracranial angiomas showed that two-thirds of the patients presented before the age of 30 years—subarachnoid haemorrhage occurred in 34%, intracerebral haemorrhage in 30%, and epilepsy in 24%. Bleeding from an arteriovenous malformation was less apt to be fatal than bleeding from an aneurysm. Malformations were often smaller and deeper than in Western series. In the latter the parietal lobes are the commonest site and in Singapore the frontal lobes. One of the major differences between the Western and Singapore cases is the much higher incidence of intracranial haemorrhage in the latter. Ransome and Gwee³⁰ found that bilateral carotid arteriography in intracranial haemorrhage, intracerebral or subarachnoid, showed the presence of an aneurysm or an arteriovenous malformation in less than 10% of cases.

It does seem, therefore, that in these countries angiomas play a greater part in the aetiology of subarachnoid haemorrhage than they do in the West. In the United Kingdom aneurysm is 9 or 10 times as common as angioma in subarachnoid haemorrhage.³¹ More statistics are required to determine the incidence of subarachnoid haemorrhage in various areas in the East and the relative roles of aneurysm and angioma.

Congenital Atlantoaxial Dislocation

This is a rare cause of neurological disability in the West; Greenberg³² estimated that there were only 94 published cases. In India, however, it is not uncommon. I was informed by a young intern in a Delhi hospital that medical students know about the syndrome and that "sometimes you can guess what is wrong when you see the patient walking up the hospital drive." Even if that is an exaggeration it does imply an unusual degree of familiarity with a condition that is rare here.

Credit for this intriguing observation goes to the Bombay neurologist, N. H. Wadia.¹¹³ Since his first report in 1960³³ there has been general confirmation of his findings in India, and to date he has seen 52 cases.³⁴ A visiting neurologist is likely to be shown examples of this disorder in most Indian neurological centres. Wadia described three main groups of symptoms: cervical pain and stiffness, transitory attacks, and progressive neurological disturbance.

Cervical symptoms rarely predominate as in acquired lesions,

and they may be absent until there has been some trivial injury to the neck. Transient attacks of paralysis are a characteristic feature. These may consist of intense paraesthesiae in the limbs, transient tetraparesis, or sudden loss of vision or consciousness. They are usually precipitated by some sudden movement of the neck. These episodes may last from 5 to 30 minutes, but a feeling of "weakness" may persist for several weeks. Wadia stressed that specific inquiry for such transient episodes should be made in all cases when there are clinical indications of a high cervical cord lesion otherwise they may not be mentioned. The ensuing disability is mainly that of a spastic tetraparesis—posterior column signs are common; sphincter difficulties are uncommon. As in other craniovertebral anomalies sometimes postural loss is greater in the upper than in the lower limbs.

Most of the patients are young males and many have a short neck. Disability is at first intermittent, but permanent motor disability may persist throughout the patient's lifetime. Careful x-ray examination is essential for diagnosis. Occipitalization of the atlas, fusion of the second and third cervical vertebrae, and an abnormal odontoid process are the main findings.

Surgical experience has shown that simple removal of the posterior arch of the atlas and the posterior margin of the foramen magnum, as performed for basilar invagination or the Arnold-Chiari malformation, is dangerous.³⁵ The dislocation should be reduced preoperatively. Thus the distinction between congenital atlantoaxial dislocation and other types of craniovertebral anomaly is an important one.

There has been no explanation for the high incidence of this type of abnormality in India, but there are suggestions that it is also frequent in Ceylon and Thailand. There are adequate necropsy studies in India and there is no evidence that the lesions are acquired.

Painful Ophthalmoplegia

In Britain a patient presenting with an acute unilateral painful ophthalmoplegia usually has an intracranial aneurysm. Not so in Vellore, South India. In 56 such cases only four were due to aneurysm. In 30 the diagnosis was "painful ophthalmoplegia."³⁶ This is the commonest type of acute ophthalmoplegia in South India. It affects males and females in a ratio of 3:1, with a maximum incidence in young adults and the middle-aged. For a few days or weeks there is pain in and about one eye and this is followed by diplopia and ptosis. Various combinations of involvement of the third, fourth, sixth, and first division of the trigeminal nerve are seen. The pupil is usually spared. Rarely, there is some hint of involvement of the optic nerve. The eyeball is tender, and there may be slight proptosis and periorbital oedema. Systemic examination shows nothing abnormal.

Untreated, it runs a self-limiting course. The pain gradually subsides after a few weeks but neurological signs may persist for several months. Recovery may not be complete and recurrence is a feature of the disease. A third of the patients described by Mathew and Chandu³⁶ had a recurrence. This is usually on the same side and it may occur within a few months or only after several years.

In the acute stage there may be a moderate rise in the sedimentation rate in some cases, otherwise investigations are negative. Carotid arteriography sometimes shows irregular narrowing of the intracavernous portion of the internal carotid artery on the affected side. A most remarkable feature of the illness is the dramatic way in which it responds to treatment with steroids. This is evident in 24 to 72 hours. Response to steroids can be used as a therapeutic test.

In Britain I have seen this syndrome of unilateral recurrent painful ophthalmoplegia on only two occasions. The first patient was a young Chinese male cook from Hong Kong and the second was a young Indian doctor. In Madras I heard of a patient in whom the illness began while he was in an aeroplane on his way to Britain. A message suggesting the probable

diagnosis and appropriate treatment was received here too late to avoid intensive investigation.

Isolated examples of this syndrome have been described in many countries, and the experience of Tolosa³⁷ and Hunt *et al.*³⁸ suggest that the pathological basis for the syndrome is a periarteritic carotid lesion, possibly the result of some immuno-allergic disturbance. But its relatively high incidence in South India is intriguing. It is remarkable that to date 34 cases have been seen in Vellore.³⁹ Its incidence in the Far East should be investigated.

Infantile Tremor Syndrome

During the past decade an infantile syndrome has been described from various parts of India, characterized by developmental retardation, apathy, hypokinesia, and the sudden onset of tremors.⁴⁰⁻⁴³ The illness affects children between the ages of 6 and 24 months. It has not been described outside India and I personally have never seen any similar illness in children in Britain. It has little resemblance to the epidemic of "encephalitis tremens" described in Western Nigeria,⁴⁴ or to the obscure progressive "new tremor syndromes" in the western highlands of New Guinea⁴⁵ or to the kwashiorkor recovery state described in South Africa.⁴⁶

Affected infants come from families in lower socioeconomic groups and are usually brought to hospital in the summer months because of the abrupt onset of generalized tremors. There is usually a preceding story of retardation and apathy for some weeks. In about half of the cases there is some fever. The infants usually look plump and well covered, noticeable malnutrition is infrequent, but they are usually pale and anaemic. The infant retains full consciousness throughout the illness but is listless, unresponsive, and tremulous. The tremors are usually generalized but are most apparent in the face, around the eyes and lips, and in the arms. The tremors are fast and of high amplitude, subside during sleep, and may be accompanied by a characteristic posture. The arms are abducted at the shoulders, flexed at the elbows and wrists, and they tremble in a manner to suggest "a bird with fluttering wings." There is no particular reflex or sensory change. The illness runs a self-limiting course of some weeks or months; it is rarely fatal but subsequent mental retardation is common.

The only notable abnormality in laboratory investigations is that of anaemia; 80% are anaemic and in nearly 50% the haemoglobin is below 8 g/100 ml. Tandon and Bajpai⁴³ found that bone marrow examination in 104 patients disclosed normoblastic hyperplasia in all except 11, who had a megaloblastic reaction. None of the infants had a serum vitamin B₁₂ level below 100 pg/ml. Examination of the cerebrospinal fluid and liver biopsy specimens showed nothing abnormal.

The electroencephalogram is abnormal in half of these cases, with multifocal or diffuse epileptic types of abnormality, and air encephalography often shows some degree of ensuing cerebral atrophy. Brain biopsy in most cases shows slight signs of inflammatory reaction in the meninges, with gliosis and astrocyte hypertrophy.

At one time there was some suspicion that this syndrome might be due to vitamin B₁₂ deficiency, but further investigations have not supported this view. Although the cause of this illness is not known it does present a striking and, in my experience, unique clinical picture. Anyone who has seen an infant in the tremor phase of the illness is unlikely to forget it.

Thyrotoxic Periodic Paralysis

In the West a new case of thyrotoxic periodic paralysis is usually fully investigated and reported.⁴⁷ It is rare and I have never seen a case in Britain. On the other hand, in a ward round in a Japanese hospital I saw two cases. One was a newly admitted

young male and the other a young female who two years previously had been rendered completely paralysed and decorticate by an insulin-carbohydrate provocation test.

Thyrotoxic periodic paralysis is well known in Japan, having been first described there in 1913 by Kitamura.⁴⁸ Engel⁴⁹ estimated that, in fact, 90% of 228 reported cases of thyrotoxic periodic paralysis were Japanese. In a series of 6,333 cases of thyrotoxicosis Okinaka *et al.*⁵⁰ found that 8.9% of the males had suffered from attacks of periodic paralysis but only 0.4% of the females. Itahara,⁵¹ in Japan, found that 71 out of 126 cases of periodic paralysis were thyrotoxic. Satoyoshi *et al.*⁵² reported that 8% of 432 patients with thyrotoxicosis had attacks of periodic paralysis. There were 87 males with thyrotoxicosis, and yet 30 of these had periodic paralysis. In contrast, only 2% of the thyrotoxic females were so afflicted.

In Hong Kong, among a series of 1,366 consecutive patients with thyrotoxicosis (1,188 females and 178 males) 25 (1.8%) had attacks of periodic paralysis⁵³; 23 of these 25 patients were males; all were Chinese.

In Singapore there were 18 cases of periodic paralysis in a series of 1,022 cases of thyrotoxicosis.⁵⁰ Only one of the 18 patients was a female and all were Chinese. In Taiwan, however, out of 28 cases of periodic paralysis only one was thyrotoxic⁵⁴; 25 were of the idiopathic variety. In Thailand Vejajiva⁵⁵ saw 12 cases of thyrotoxic periodic paralysis in five years.

It does, therefore, appear that there is a peculiar susceptibility to thyrotoxic periodic paralysis in the Japanese, Chinese, and Thai members of the Mongolian race. Curiously, familial periodic paralysis in these races appears to be rarer than in the West—one family in the Japanese series,⁵⁰ two families in the Hong Kong series,⁵³ two families in Taiwan,⁵⁴ and one family in Thailand.⁵⁵

There is general agreement in these reports from the Far East that the attacks of periodic paralysis in thyrotoxicosis do not differ from the sporadic and familial hypokalaemic forms with which we are familiar in the West. In both types there is a preponderance of males, factors which induce attacks are the same, and the biochemical changes are similar—hypokalaemia and retention of water and sodium.

In thyrotoxicosis the occurrence of paralysis is not related to the duration or severity of the endocrine disorder. The thyrotoxic patients tend to be older, the family history is negative, and attacks of periodic paralysis do not occur and cannot be induced when the patient becomes euthyroid. In both the familial and thyrotoxic forms of periodical paralysis there is the same vacuolization of the muscles during paralysis.^{52, 56} Hypokalaemia is not the sole cause of paralysis in either case because the magnitude of the potassium ion shifts is not consistent with the degree of clinical paralysis, and the serum potassium concentrations do not rise as the paralysis subsides.⁴⁷ Electromyographic studies indicate that the paralysis in both forms results from an acute myopathy. Future studies must be directed to the nature of the genetic predisposition to periodic paralysis and to the systemic factor which induces the paralysis.

Juvenile Motor Neurone Disease

Motor neurone disease is a disease of late middle life, so I was surprised to learn that in Madras Professor K. Jagannathan referred to a juvenile form. In South India generally it is well known and does not differ clinically or pathologically from the classical forms which we know—progressive muscular atrophy, amyotrophic lateral sclerosis, and chronic bulbar palsy. But in Madras 10% of the patients develop the disease before the end of the third decade. During the years 1966-70 there were 14 patients with an average age onset of 15 years.⁵⁷ I saw several of these patients.

There are no necropsy studies as yet, but in addition to the young age of onset there are other unusual features. The first of these is the high incidence of involvement of cranial nerve nuclei—60%. This is not a late development as is so often the

case in the West but an early one. Bilateral weakness of the facial muscles is common. Weakness of the palate and wasting and conspicuous fasciculation of the tongue may be observed in the early stages of the illness. Secondly, Jagannathan reports that in about a third of these juvenile cases there is some degree of bilateral perceptive deafness. No cause for this has been found. Thirdly, the disease tends to pursue a more chronic course than the classical forms. Although in the West we have come to appreciate that there is a wide variation in the rate of progress of this disease in all its manifestations, those who develop progressive bulbar palsy seldom survive more than three years. Many of the Madras patients seem able to continue at work for some years. Limb involvement may remain asymmetrical for several years but with characteristic fasciculation, clawing of the hands, foot-drop, hyperactive reflexes, and extensor plantar responses.

In this juvenile form the family history is negative, no evidence of intoxication or occupational aetiology has been discovered, and electromyography and muscle biopsies have shown the characteristic features of neurogenic muscular atrophy.

Thus we appear to be dealing with a disease which can be differentiated from chronic spinal muscular atrophy of childhood and adolescence and from the rare familial form of motor neurone disease.

Multiple Sclerosis

Impressions of an uneven geographical distribution of multiple sclerosis were first expressed 50 years ago, and epidemiological surveys in recent years have established that there are high-risk, medium-risk, and low-risk areas. Acheson⁵⁸ defined a high-risk zone as one with a prevalence rate of more than 40 per 100,000 population and noted that there was no such zone between latitudes 40°N and 40°S. Most studies have been conducted in the northern hemisphere, but a similar pattern appears to be emerging in the southern hemisphere.^{59, 60} In the high-frequency band (30 to 60 per 100,000) are Western Europe, the Northern United States, and Southern Canada. In the medium-frequency band (5 to 15 per 100,000) lie the Southern United States, Southern Europe, and Australia. Low-frequency areas (0 to 4 per 100,000) include Israel, Africa, and Japan.⁶¹ It has recently been shown that in Mexico the prevalence rate is only 1.6 per 100,000, among the lowest reported anywhere in the world.⁶² In Denmark the rate is 64 per 100,000, one of the highest.⁶³ In England it is 50 per 100,000.⁶⁴

With regard to geographical longitude there is some evidence that the disease apparently diminishes with increasing east longitude from Western Europe to Eastern Siberia.^{65, 66} In the eastern parts of the U.S.S.R., North Korea, and China there appears to be a relatively low prevalence of the disease despite the high geographical latitude. In Japan the prevalence rate is only 2 to 4 per 100,000; no difference in respect of latitude has been discovered there.^{67, 68} These Japanese figures include all cases of neuromyelitis optica (Devic's disease), which is increasingly regarded as an acute form of multiple sclerosis. It is common in Japan and accounted for one in every 10 cases of multiple sclerosis in these Japanese series; it is rare in the United Kingdom. In Japan it is characterized by acute bilateral retrobulbar neuritis and acute myelitis. These lesions may develop simultaneously or one may follow the other after a short interval. Retrobulbar neuritis itself is usually (77%) bilateral in Japan, whereas in the United Kingdom it is usually unilateral.

These differences in the prevalence, distribution, and clinical expression of multiple sclerosis in Japan are intriguing and need to be studied closely. Most Japanese neurologists have the impression that the classical, remitting form of the disease as we know it in the West is being increasingly recognized, and some think that this is the result of a genuine rise in incidence.

What happens when people born in a high-risk area emigrate? Studies in South Africa,⁶⁹⁻⁷¹ Israel,^{72, 73} the Dutch Antilles,⁷⁴ Hawaii,^{75, 76} and the United States⁷⁷⁻⁷⁹ show that immigrants

tend to retain the prevalence rate of their country or state of origin. Studies in Australia and Tasmania⁵⁹⁻⁸² and in New Zealand⁶⁰ confirm the relation between latitude and prevalence observed in the northern hemisphere but do not appear to indicate that European immigrants have higher rates than native-born Australians. Elsewhere in the world data on the effect of age of migration on the risk of developing multiple sclerosis indicate that the critical age is near puberty. Emigration before 15 years reduces the risk.

What do these observations mean? What does the immigrant carry with him to a low-risk zone which determines his chances of developing the disease? We do not know whether multiple sclerosis is an infection but let us assume it is. Does early exposure in a low-risk area afford some immunity? If this were true we might expect that the "unexposed" immigrants would show a much higher attack rate than prevails in their country of origin. This does not appear to be the case.

Alternatively these studies of multiple sclerosis in migrant populations might be taken to indicate that the disease is "caught" at about the age of 15 and that there is a latent interval before clinical expression. In discussing these interpretations, Dean and Kurtzke,⁷¹ who adopt the first and second hypotheses respectively, agree that the most likely aetiological candidate is a virus.

If multiple sclerosis is not an infective disease these epidemiological data are even more enigmatic. The patient with multiple sclerosis is usually to be found in a temperate environment, but the agent within is unknown. It remains to be seen whether it is *where* he lives or *how* he lives that matters most.

Neurological Diseases in Guam

Guam is one of the Mariana Islands in the West Pacific, midway between Japan and New Guinea and a territory of the U.S.A. Although it is only 30 miles (48 km) long and four to nine miles (6 to 14 km) wide, with a native population of 40,000, it has come to occupy a unique place in neurological literature because it is a focus of two major neurological diseases which occur at an extraordinarily high rate. These diseases are motor neurone disease (amyotrophic lateral sclerosis) and the Parkinsonism-dementia syndrome. A high incidence of the former disease in Guam was first noted in 1945, and during the following decade investigations led to the discovery of the Parkinsonism-dementia syndrome in 1954 and to the establishment of a research centre by the National Institutes of Health, U.S.A., in 1956.⁸³⁻⁸⁴

In Europe and North America the prevalence rate of amyotrophic lateral sclerosis is about 6 per 100,000; in Guam the rate is 100 per 100,000. The Parkinsonism-dementia syndrome is a unique disease and has not been described elsewhere, but the prevalence rate in Guam is 87 per 100,000.⁸⁵ These two diseases account for 20% of deaths among Guamanians over age 20.⁸⁶ These observers have never found multiple sclerosis or classical paralysis agitans in the natives of Guam. Other foci of amyotrophic lateral sclerosis have not been uncovered in other islands of Micronesia, although Japanese investigators have detected a focus in the Kii Peninsular of Japan.⁸⁷ In comparison with other populations the residents of Guam have higher rates of convulsive disorders, myotonic dystrophy, peroneal muscular atrophy, and hereditary ataxias.⁸⁸

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis in Guam resembles the classical picture seen in other areas of the world in the mean age at onset, the mean survival time, and the excess of male over female patients. In Guam, however, there are more patients under the age of 40 and more patients who survive 10 or more years than elsewhere. Pathological studies have shown that in addition to the classical findings of this disease there are certain distinctive features.⁸⁸⁻⁸⁹ These consist of neurofibrillary changes and

granulovacuolar bodies. Originally, because the disease was thought to be confined to the Chamorro linguistic group and because family aggregations were noted, often over several generations, a genetic hypothesis was proposed. But it seems that there may also be a similar high incidence of the disease in other populations in the Western Pacific islands, and Kurland⁹⁰ feels that a toxic nutritional agent which may be superimposed on genetic predisposition offers a reasonable explanation.

PARKINSONISM-DEMENTIA SYNDROME

The cardinal clinical features of this disease are progressive organic dementia and striatal disturbances in the form of bradykinesia, rigidity, or tremor. Amnesia, disorientation, and personality change are followed or accompanied by slurring of speech, slowing of gait, rigidity of trunk and limbs, and tremors.

The pathological findings were cerebral atrophy, degeneration of the substantia nigra and the globus pallidus, with widespread neurofibrillary changes in certain parts of the nervous system and granulovacuolar bodies. In addition there were features which occur in amyotrophic lateral sclerosis—namely, involvement of the motor neurones and pyramidal tracts.

As in the classical form of Parkinsonism there is depressed dopamine synthesis in the nervous system in the Guam cases.⁹¹ A similar disturbance, as measured by the level of homovanillic acid in the spinal fluid, has also been detected in cases of amyotrophic lateral sclerosis in Guam.⁸⁶

These exceptionally interesting neurological discoveries remain a mystery. Intensive investigations have not disclosed any definite pattern of inheritance, there is no evidence of any form of slow virus infection, and no neurotoxin has been identified. Guamanians in California have the same high frequency of amyotrophic lateral sclerosis but not of the Parkinsonism-dementia syndrome.

Subacute Myelo-optic neuropathy in Japan

During 1960-70 Japanese physicians and pathologists identified this new neurological disease. In the earlier reports titles such as the following were used. "Paraplegia during the course of enterocolitis, Haemorrhagic diarrhoea accompanying polyneuritic syndrome, Encephalomyelopathy with prodromal enteric disorder, Autopsy cases of paralytic patients following abdominal symptoms, and Multiple sclerosis-like syndrome following abdominal symptoms." In 1964 the Japanese Society of Internal Medicine held a symposium on "Non-specific encephalomyelitis,"⁹² in which clinicians from various parts of the country described the clinical and pathological features of their cases. It was at this meeting that Tsubaki *et al.*⁹³ proposed the name subacute myelo-optic neuropathy (S.M.O.N.). On the basis of 823 cases with 26 necropsy reports there was general agreement at the symposium that they were dealing with a new entity. In the next few years cases were recognized with increasing frequency, especially during the late summer months, and there were severe outbreaks in 1967 and 1969. A research commission was set up in 1969 and the annual incidence of the disease was found to be as follows: 1966, 1,172; 1967, 1,276; 1968, 1,743; 1969, 1,988.⁹⁴

Subacute myelo-optic neuropathy is mainly a disease of adults; children are rarely affected. Older people, especially women, seem particularly susceptible. Many patients had already suffered from some form of chronic abdominal complaint, usually with diarrhoea. Those who developed the disease were often already in hospital for investigation or treatment and many had undergone laparotomy. The actual neurological disorder, however, was also nearly always preceded by prodromal abdominal symptoms; pain was the main feature of this phase of the illness. It was often severe and colicky and

sometimes accompanied by constipation and ileus but not diarrhoea. It was difficult to relieve.

It was generally agreed that the prodromal abdominal symptoms were fairly characteristic but that in those patients who suffered from chronic abdominal complaints the features were not distinctive. There were variations on this theme. Sometimes there was no story of previous abdominal illness; the prodromal abdominal symptoms were often mild and occasionally absent entirely; distinction between the chronic and the prodromal abdominal complaints was not always possible. The prodromal symptoms usually lasted several days or weeks.

The onset of the neurological disorder was acute in 60% and subacute in 40%. This was largely sensory. The patient complained of the rapid development of numbness and paraesthesiae, usually beginning in the feet and ascending to the trunk and not often involving the upper limbs. Occasionally numbness was first noticed around the waist and later involved the lower limbs. The paraesthesiae took various forms. Quite often they consisted merely of numbness and tingling, but many patients described more unpleasant sensations, some of them painful—thorns in the feet, gravel between the toes, pebbles in the shoes, and so on. Others felt that they were "walking on air or on felt, sponges or rubber." These sensations rose, usually to L1 or T10 levels, in a matter of days or weeks. There was little fluctuation at this stage, but in some there appeared to have been temporary improvement and then a return of symptoms. A degree of ataxia was noted by the majority. In some actual pain was severe, while in others there was diffuse cutaneous hyperaesthesia and hyperalgesia. Sensory distortion was frequently noted.

With these sensory symptoms ataxia was commonly described and observed. Some patients were soon severely disabled and unable to stand without support. In others disability was largely due to muscular weakness. On the whole sensory ataxia was more common and more obvious than muscular weakness. The latter was present in about half of the patients, but reflex abnormality in the lower limbs was present in most. A common combination was hyperactive knee jerks and absent ankle jerks together with superficial sensory loss, most pronounced distally, with loss of vibration and postural appreciation. Ankle clonus and extensor plantar responses were seen in about 8%. Complete paraplegia occurred in about 11% and bladder disorders in about 16%. The only cranial nerve commonly affected was the optic; about a quarter of the patients complained of loss of vision and 5% developed optic atrophy.

Recovery was slow. About half were well in one or two years, 10% to 15% were completely disabled, and there was a fatality rate of between 3% and 5%. Blindness occurred in 2% to 3%. Some patients relapsed in a year or so, and in many, although there was full recovery of motor function, numbness and some form of dysaesthesiae persisted indefinitely.

Laboratory investigations were largely negative; blood and spinal fluid were normal. Electromyography, nerve conduction studies, and nerve biopsies showed characteristic features of segmental demyelination.

At necropsy the only appreciable visceral lesion was occasional atrophy of the intestinal or colonic mucosa. In the nervous system, however, demyelinating lesions were found in the posterior columns of the spinal cord, the pyramidal tracts, and sometimes in the optic nerves or chiasma.⁹⁵ Degenerative changes were seen in the ganglion cells of the lumbar and dorsal root ganglia, with axonal degeneration proximally and distally. Demyelination of the spinal cord was most apparent in the lower thoracic and upper lumbar levels. The posterior columns were almost invariably involved, and changes in the pyramidal pathways were less common and prominent. In the posterior columns the upper levels were most involved and in the pyramidal tracts the lower levels. Degenerative lesions were also seen in autonomic nerves, especially in the distal portions of the vagus and sympathetic. There were no noticeable alterations in Auerbach's plexus.⁹⁶ In the nervous system as a whole there was scarcely any sign of an inflammatory reaction.

An infectious aetiology was suspected because of the way in which outbreaks of the disease would occur in different towns and areas, usually in the summer months, and because they were so often associated or accompanied by an intestinal disorder. On the other hand, fever, rash, and changes in blood and spinal fluid were not observed. Children were rarely affected and case-to-case contact was rarely noted. The pathological changes in the spinal cord and peripheral nerves did not suggest an infectious agent. From time to time there were reports of alteration of the intestinal flora and various viruses, new and old, were indicted. But general confirmation was lacking. There was no evidence of industrial or occupational aetiology.

When the first clinicopathological account of this new neurological disorder was sent for publication in the West in May 1970 the aetiology remained obscure.⁹⁷ The clue came when it was found that some patients had a greenish fur on the tongue.⁹⁸ A pseudomonal infection was suspected but not confirmed. A few months later two patients were noted to have greenish urine.⁹⁹ Subsequent investigations showed that the green pigment on the tongue and in the urine (and also in the faeces) proved to be an iron chelate of clioquinol (5-chloro-7-iodo-8-hydroxyquinoline). Crystals of free clioquinol were also found in the urine. Inquiries then raised the possibility that the disease might result from clioquinol intoxication. Tsubaki *et al.*¹⁰⁰ found that 166 out of 171 patients with subacute myelo-optic neuropathy had received the drug before neural symptoms appeared (96%). They compared the incidence of neurological symptoms in patients with gastrointestinal disorders with and without clioquinol treatment. In 263 patients who had clioquinol treatment there were 44 cases of subacute myelo-optic neuropathy (17%). In 706 patients who had not received clioquinol treatment there were no neurological complications.

Retrospective studies organized by the S.M.O.N. Research Commission showed that 85% of the patients had had treatment with clioquinol in the six months before the onset of the neurological disorder. It was shown that the disease tended to occur in hospitals where clioquinol was freely prescribed and that the dosage and duration of treatment with clioquinol was related to the development and severity of the neurological illness.^{101 102} No other factor seemed to be of importance in determining whether a patient with an enteric disorder would develop subacute myelo-optic neuropathy. Neither the nature of the illness nor the mode of medical or surgical treatment nor the type of antibiotic used seemed to be determining factors.

During 1970 new cases continued to be recognized by the research commission each month. About 35 a month in January, February, and March; 45 in April; 48 in May; 57 in June; 60 in July; 48 in August; 26 in September; and fewer than 10 in the remaining months of that year. There were 1,135 cases in 1970 up to the end of October.⁹⁸ The clioquinol hypothesis was presented by Tsubaki on 7 August 1970 and the Ministry of Health banned the sale of the drug on 8 September. So the incidence of the disease that summer began to decline two months before the ban on clioquinol. Professor Kono informs me (March 1972) that the commission has recognized only 15 cases during 1971.

Clioquinol has been widely used throughout the world for various forms of diarrhoea during the past 30 years and neurotoxic side effects seem to be rare. Formerly it was thought that the drug was not absorbed; now we know it is. But if clioquinol neurotoxicity is the whole story of this disorder we are still dealing with something mysterious. If it transpires that the disease is rare outside Japan what is the explanation? Is the missing factor a genetic one or another environmental agent? Are we dealing with intestinal interaction between clioquinol and some other substance, viral or non-viral? Or will the disease be recognized in those areas of the world where clioquinol is perhaps used in an extravagant manner. We are unlikely to see it on any scale in Britain, but six cases have been reported from Australia,¹⁰³ and the drug evaluation committee has recommended that drugs of this group (the halogenated

oxyquinolines) should be made available only on a doctor's prescription.

Experimental studies with clioquinol^{101 104} and with a virus grown from patients with subacute myelo-opticneuropathy¹⁰⁵⁻¹⁰⁸ have been shown to produce degeneration in the posterior columns and pyramidal tracts of the spinal cord, in the peripheral nerves, and in the optic chiasma of certain animals.

It is difficult to believe that clioquinol is not involved in the aetiology of this new disease, but other factors must clearly be investigated.

References

- Hillary, W., *Observations on the Changes of the Air and the Concomitant Epidemic Diseases, in the Island of Barbados*. London, C. Hitch and L. Hawes, 1759.
- Casal y Julian, C., *Historia natural, y medica de el Principado de Asturias*. Madrid, M. Martin, 1762.
- Rutty, J., *A Chronological History of the Weather and Seasons, and of the Prevaling Diseases in Dublin*. London, Robinson and Roberts, 1770.
- Winterbottom, T. M., *An Account of the Native Africans in the Neighbourhood of Sierra Leone*. London, New Sydenham Society, 1803.
- Hirsch, A., *Handbuch der historisch-geographischen Pathologie*. Erlangen, 1860.
- Sigerist, H. E., in *A History of Medicine*, vol. 1, p. 58. London, Oxford University Press, 1951.
- Schwidde, J. T., *American Journal of Diseases of Children*, 1952, **84**, 35.
- Ingraham, F. D., and Swan, H., *New England Journal of Medicine*, 1943, **228**, 559.
- Laurence, K. M., personal communication, 1970.
- Suwanwela, C., and Hongsaprabhas, C., *Journal of Neurosurgery*, 1966, **25**, 172.
- Suwanwela, C., *Excerpta Medica. International Congress Series*, 1969, No. 193, p. 158.
- Flatz, G., and Sukthomya, C., *Humangenetik*, 1970, **11**, 1.
- Penrose, L. S., *Journal of Mental Deficiency Research*, 1957, **1**, 1.
- Simpkiss, M., and Lowe, A., *Archives of Disease in Childhood*, 1961, **36**, 404.
- Odeku, E. L., *International Surgery*, 1967, **48**, 52.
- Lorber, J., *Archives of Disease in Childhood*, 1961, **36**, 381.
- Norman, A. P., *Congenital Abnormalities in Infancy*, p. 21. Oxford, Blackwell Scientific, 1963.
- Ingraham, F. D., and Matson, D. D., *Neurosurgery of Infancy and Childhood*, p. 456. Springfield, Illinois, Thomas, 1954.
- Dekaban, A., *Neurology of Infancy*, p. 181. Baltimore, Williams and Wilkins, 1959.
- Tandon, P. N., *Neurology (Bombay)*, 1966, **14**, 161.
- Tandon, P. N., *Acta Neurologica Scandinavica*, 1970, **16**, 369.
- Tandon, P. N., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Chitanondh, H., personal communication, 1965.
- Selby, G., *Lancet*, 1972, **1**, 123.
- Ramamurthi, M., *Excerpta Medica. International Congress Series*, 1969, No. 193, p. 149.
- Ramamurthi, M., personal communication, 1969.
- Dastur, H. M., personal communication, 1970.
- Suwanwela, C., Suwanwela, N., Hongladarom, T., and Hongsaprabhas, C., *Chulalongkorn Medical Journal*, 1969, **14**, 56.
- Tay, C. H., Oon, C. L., Lai, C. S., Loong, S. C., and Gwee, A. L., *Brain*, 1971, **94**, 61.
- Ransome, G. A., and Gwee, A. L., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Brain, Lord, and Walton, J. W., *Brain's Diseases of the Nervous System*, 7th edn. London, Oxford University Press, 1969.
- Greenberg, A. D., *Brain*, 1968, **91**, 655.
- Wadia, N. H., *Neurology (Bombay)*, 1960, **8**, 81.
- Wadia, N. H., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Dastur, D. K., Wadia, N. H., Desai, A. D., and Sinh, G., *Brain*, 1965, **88**, 897.
- Mathew, N. T., and Chandy, J., *Journal of the Neurological Sciences*, 1970, **11**, 243.
- Tolosa, E., *Journal of Neurology, Neurosurgery and Psychiatry*, 1954, **17**, 300.
- Hunt, W. E., Meagher, J. N., Lefever, H. E., and Zeman, W., *Neurology (Minneapolis)*, 1961, **11**, 56.
- Mathew, N. T., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Pohowalla, J. N., Kaul, K. K., Bhandari, N. R., and Singh, S. D., *Indian Journal of Pediatrics*, 1960, **27**, 49.
- Sachdeva, K. K., Manchanda, S. S., and Lal, H., *Indian Pediatrics*, 1965, **2**, 239.
- Bajpai, P. C., Tandon, P. N., Sharma, N. L., and Misra, P. K., *Acta Neurologica Scandinavica*, 1965, **41**, 473.
- Tandon, P. N., and Bajpai, P. C., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Wright, J., and Morley, D. C., *Lancet*, 1958, **1**, 871.
- Wilson, K., Zigas, V., and Gajdusek, D. C., *Lancet*, 1959, **2**, 699.
- Kahn, E., *Archives of Disease in Childhood*, 1954, **29**, 256.
- Norris, F. H., Clark, E. C., and Biglieri, E. G., *Journal of the Neurological Sciences*, 1970, **13**, 431.
- Kitamura, K., quoted by Norris et al.⁴⁷
- Engel, A. G., *American Journal of Medicine*, 1961, **30**, 327.
- Okinaka, S., et al., *Journal of Clinical Endocrinology*, 1957, **17**, 1454.
- Itahara, K., *Clinical Neurology*, 1961, **1**, 450.
- Satoyoshi, E., et al., *Neurology*, 1963, **13**, 645.
- McFadzean, A. J. S., and Yeung, R., *British Medical Journal*, 1967, **1**, 451.
- Chen, K. M., Hung, T. P., and Lin, T. Y., *Archives of Neurology*, 1965, **12**, 165.
- Vejajiva, A., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Norris, F. H., Panner, B. J., and Stormont, J. M., *Archives of Neurology*, 1968, **19**, 88.
- Jagannathan, K., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Acheson, E. D., *Medical Journal of Australia*, 1963, **1**, 556.
- McCall, M. G., et al., *Journal of Neurology, Neurosurgery and Psychiatry*, 1968, **31**, 1.
- Hornabrook, R. W., *Acta Neurologica Scandinavica*, 1971, **47**, 426.
- Kurtzke, J. F., *Acta Neurologica Scandinavica*, 1966, **42**, Suppl. No. 19, p. 91.
- Alter, M., and Olivares, L., *Archives of Neurology*, 1970, **23**, 451.
- Hyllested, K., *Acta Psychiatrica Scandinavica*, 1960, **35**, Suppl. No. 147, p. 158.
- Poskanzer, D. C., Schapira, K., and Miller, H., *Journal of Neurology, Neurosurgery and Psychiatry*, 1963, **26**, 368.
- Barlow, J. S., *Neurology (Minneapolis)*, 1967, **17**, 802.
- Barlow, J. S., *Neurology (Minneapolis)*, 1971, **21**, 353.
- Okinaka, S., et al., *Acta Neurologica Scandinavica*, 1966, **42**, Suppl. No. 19, p. 68.
- Kuroiwa, Y., in *Zukunft der Neurologie*, p. 70. Stuttgart, Thieme, 1967.
- Dean, G., *British Medical Journal*, 1949, **1**, 842.
- Dean, G., *British Medical Journal*, 1967, **1**, 724.
- Dean, G., and Kurtzke, J. F., *British Medical Journal*, 1971, **2**, 725.
- Alter, M., Halpern, L., and Kurland, L. T., *Archives of Neurology*, 1962, **7**, 253.
- Alter, M., Leibowitz, U., and Halpern, L., *Acta Neurologica Scandinavica*, 1966, **42**, Suppl. No. 19, p. 47.
- Moffie, D., *Nederlandsch Tijdschrift voor Geneeskunde*, 1966, **110**, 1454.
- Kuroiwa, Y., and Okihira, M. M., *Hawaii Medical Journal*, 1969, **28**, 374.
- Alter, M., Okihira, M., Rowley, W., and Morris, T., *Neurology (Minneapolis)*, 1971, **21**, 122.
- Alter, M., *Neurology (Minneapolis)*, 1971, **21**, 438.
- Brody, J. A., and Detels, R., *Neurology (Minneapolis)*, 1971, **21**, 445.
- Kurtzke, J. F., Kurland, L. T., and Goldberg, I. D., *Neurology (Minneapolis)*, 1971, **21**, 438.
- Saint, E. G., and Sadka, M., *Medical Journal of Australia*, 1962, **2**, 249.
- Rischbieth, R. H., *Medical Journal of Australia*, 1966, **1**, 774.
- Sutherland, J. M., Tyrer, J. H., Eadie, M. J., Casey, J. H., and Kurland, L. T., *Acta Neurologica Scandinavica*, 1966, **42**, Suppl. No. 19, p. 37.
- Mulder, D. W., Kurland, L. T., and Iriarte, L. L. G., *United States Armed Forces Medical Journal*, 1954, **5**, 1724.
- Hirano, A., Kurland, L. T., Krooth, R. S., and Lessell, G., *Brain*, 1961, **84**, 642.
- Chen, K. M., Brody, J. A., and Kurland, L. T., *Archives of Neurology*, 1968, **19**, 573.
- Brody, J. A., and Kurland, L. T., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, 1972.
- Araki, M., Kimura, K., and Yase, Y., *Excerpta Medica. International Congress Series*, 1966, No. 100, p. 219.
- Hirano, A., Malamud, N., Elizan, T. S., and Kurland, L. T., *Archives of Neurology*, 1966, **15**, 35.
- Hirano, A., Malamud, N., Kurland, L. T., and Zimmerman, H. M., in *Motor Neuron Disease*, ed. F. H. Norris and L. T. Kurland, vol. 2, p. 51. New York, Grune and Stratton, 1969.
- Kurland, L. T., in *The Central Nervous System*, ed. O. T. Bailey and D. E. Smith, p. 225. Baltimore, Williams and Wilkins, 1968.
- Brody, J. A., Chase, T. N., and Gordon, E. K., *New England Journal of Medicine*, 1970, **282**, 947.
- Kusui, K., *Japanese Journal of Medicine*, 1965, **4**, 177.
- Tsubaki, T., Tiyojura, Y., and Tsukagoshi, H., *Japanese Journal of Medicine*, 1965, **4**, 181.
- Kono, R., *Japanese Journal of Medical Science and Biology*, 1971, **24**, 195.
- Shiraki, H., *Japanese Journal of Medical Science and Biology*, 1971, **24**, 217.
- Maeda, K., *Mie Medical Journal*, 1970, **14**, 209.
- Sobue, I., et al., *Neurology (Minneapolis)*, 1971, **21**, 168.
- Takasu, T., Igata, A., and Toyokura, quoted by Kono.⁹⁴
- Igata, A., Hasegawa, S., and Tsuji, T., quoted by Kono.⁹⁴
- Tsubaki, T., Honma, Y., and Hoshi, M., *Lancet*, 1971, **1**, 696.
- Nakae, K., Yamamoto, S., and Igata, A., *Lancet*, 1971, **2**, 510.
- Igata, A., *Lancet*, 1971, **2**, 43.
- Selby, R., in *Tropical Neurology*, ed. J. D. Spillane. London, Oxford University Press, in press.
- Tateishi, J., Kuroda, S., Saito, A., and Otsuki, S., *Lancet*, 1971, **2**, 1263.
- Inoue, Y. K., Nishibe, Y., and Nakamura, Y., *Lancet*, 1971, **1**, 854.
- Inoue, Y. K., *Lancet*, 1971, **2**, 1265.
- Nakamura, Y., and Inoue, Y. K., *Lancet*, 1972, **1**, 223.
- Shimada, Y., and Tsuji, T., *Lancet*, 1971, **2**, 41.
- Khanna, K. K., and Prasad, L. S. N., *Indian Journal of Paediatrics*, 1967, **34**, 63.
- McKeown, T., and Record, R. G., in *Ciba Foundation Symposium on Congenital Malformations*. London, Churchill, 1958.
- Alter, M., *Archives of Neurology*, 1962, **7**, 411.
- Neel, J. V., quoted by McKeown and Record.¹¹⁰
- Wadia, N. H., *Brain*, 1967, **90**, 449.