Experience with the differential diagnosis and prevalence of dementing illness in India

Noshir H. Wadia

Department of Neurology, Jaslok Hospital and Research Centre, 15 Dr G. Deshmukh Marg, Bombay 400 026, India

The problem of dementia of the Alzheimer's type is considered within the broader context of a comprehensive clinical–pathological differential diagnosis of dementing illnesses of human subjects. The classification is primarily based upon chronological age groups, in which prevalence rates for various dementias differ substantially, and secondarily upon etiologic mechanisms. The approach is personalized, reflecting the authors clinical experience and the available Indian literature, which is summarized in tabular form. While pointing out the lack of basic information as to prevalence, the author believes that dementing illnesses of the growing older population of Indians will become a major medical and social problem and which, therefore, merits additional research by the Indian scientific community.

PUBLISHED experience of established Indian neurologists regarding dementia and dementing illnesses, though useful, has been small, few and somewhat dated[1–4], and no epidemiological survey has yet been made. It is nevertheless heartening to note the increasing interest in the study of these diseases amongst Indian neurologists, neuropathologists, and psychiatrists. There is an increasing need for more research, including the related subjects of biological ageing of the nervous system and care of the aged. Cross cultural perspectives should be stressed. The establishment of the Tropical Health Foundation in Ernakulum, Kerala (with the avowed objective of study and care of the aged, particularly those with dementia), the Centre for Ageing Research in New Delhi, and the WHO Multi-Centre Project on cognitive impairment and dementia in developed and developing countries (with a centre in Madras) are some examples which augur well for the future. It seems then that a review of the subject even within 5 to 7 years will yield a wealth of information equal to all that has ever been written about dementia in India so far or stated here. The account given here is personalized, being based upon my own clinical experience, and information gathered from the published Indian literature.

Definition

Dementia can be defined as a progressive deterioration of intellect, memory and thought due to organic disease of the brain, or as a lowering of the previously attained cognitive functions to a degree sufficient to interfere with the activities related to daily living and work. Memory loss, intellectual impairment, change in personality, apraxia, agnosia, visuospatial impairment, disorientation, etc., would indicate it. Using these definitions, I have excluded acute dementias, as for example, due to an occlusion of an anterior cerebral artery, or conditions like mental retardation due to birth injury, intrauterine infection, Down's syndrome, cretinism, or other conditions where there is essentially a failure to reach the normally attained cognitive functions.

Prevalence

There are a large number of causes of dementia. In Table 1 some simplification is attempted so as to allow a practical approach to a patient in whom dementia is a dominant feature. Though dementing diseases are seen at all ages, some manifest most often at a certain stage of life. For example, a variety of inherited metabolic and genetic diseases like tuberosclerosis (epiloia) cause dementia in the early years, whilst conditions like Alzheimer's disease and multiinfarct dementia occur at the other end of the life span. Hence, age of the patient is an important consideration when coming to a diagnosis of a disease causing dementia and is a useful approach to classification.

There is no reason to believe from personal experience or from the available published literature that the prevalence and types of dementing illnesses are significantly different from those seen in the West, except perhaps those related to infections of the brain like subacute sclerosing panencephalitis (SSPE) or those due to environmental factors such as pellagra.

No population-based prevalence study of dementia at all ages has been carried out in India, and indeed this would be an enormous exercise in any part of the world, given the wide variety of causative disorders and the difficulty in arriving at an accurate aetiological diagnosis. However, a small selective age-related survey in a little town of South India with a population of 18,721 revealed that there were 861 persons above the age of 60 years; of 181 such subjects randomly selected,

Table 1. Some disorders causing progressive dementia

Age 1–15 years

Inherited disorders Tuberosclerosis, Wilson's disease, leukodystrophies (metachromatic, megancephalic adrenal, Schilder's disease), ceroid lipofuscinosis, Hallervorden Spatz disease, cerebrotendinous xanthomatosis Lafora body myoclonic epilepsy, mucopolysaccharidosis, GM_2 gangliosidosis

Others Brain tumours, progressive hydrocephalus (aqueduct stenosis, post tuberculous meningitis, etc.), subacute sclerosing panencephalitis, lead poisoning

Age 16–55 years

Brain tumours and chronic obstructive hydrocephalus (acoustic neuroma, colloid cyst of third ventricle, slow midline tumours, aqueduct stenosis), normal pressure hydrocephalus

Infections Neurosyphilis, cysticercosis, Creutzfeldt–Jakob disease, AIDS, Whipple's disease

Acquired metabolic Myxoedema, vitamin B_{12} deficiency, pellagra, hypercalcemia, chronic hypoglycemia, renal and dialysis encephalopathy, steroid-induced, hepatocerebral degeneration

Toxic Alcohol (Korsakoff's psychosis, alcoholic dementia), mercury, arsenic, manganese, chronic barbiturate intoxication

Degenerative Huntington's disease, Parkinson's disease, Steele Richardson Olzewski's disease (progressive supranuclear palsy), Down's syndrome with delayed cognition impairment

Trauma Chronic subdural haematoma, dementia pugilistica
Intracranial vasculitis and microangiopathy
Nonmetastatic complication of overt and occult malignancy

Age 56 years and above

Alzheimer's disease, multiinfarct dementia, Pick's disease, subcortical arteriosclerotic encephalopathy (Binswanger's disease)

11 were found to be demented[5]. In another geropsychiatric survey in Tiruppuvanam near Madurai (South India), 686 persons over 60 years were screened; a 'chronic organic brain syndrome' amounting to dementia was found[6] in 10%. These figures are comparable to those reported from the West and reflect the relatively high prevalence of demented among older subjects. No breakdown above 60 years is available, however, to tell us if the proportion of dements increases with each succeeding decade over 60 years, as is the case in the developed world.

The relative frequency of various dementing diseases is not accurately known, but estimates can be derived from the publication of Wells[7] (Table 2) who compiled data from four neurological centres (including his own) in the United States. Four reports[1–4] mention the various causes of dementia (Tables 3–6) observed in the Indian population. Though useful, the first three studies[1–3] were small, retrospective and not backed by autopsy examinations. The fourth study rectified this deficiency somewhat by reporting neuropathologic findings of 10 autopsies from a group of the 60 clinically analysed patients.

It is worth noting that Srinivas *et al.*[4] (Table 6) could not arrive at a specific clinical diagnosis in 42 of their 60 cases and had to be satisfied with diagnostic labels of pre-senile dementia (40–59 years), senile dementia (60 years and above), and 'type unknown' (below 40 years). Pathological examination of three patients in the pre-senile and senile groups revealed multiple infarctions in two and the adult variety of ceroid lipofuscinosis (Kuff's type) in one. Of the three 'unknown type' cases below the age of 40 years who came to autopsy, one had Hallervorden–Spatz disease, another had the adult form of ceroid lipofuscinosis and the third could not be diagnosed. This experience illustrates the considerable difficulty in arriving at a specific diagnosis based upon clinical examination alone. Of the 18 in whom the diagnosis was made clinically, four came to autopsy. In these four cases, the clinical diagnosis was confirmed as general paresis of the insane (GPI) and multiinfarct dementia in two each, suggesting that such patients can be more easily diagnosed. One of the cases of multiinfarct dementia seems to have been reclassified as Binswanger's disease

Table 2. Relative frequency of common dementing diseases

Dementing diseases	Relative frequency (%)
Cerebral atrophy, mainly Alzheimer – senile dementia	50
Multiinfarct dementia	10
Alcoholic dementia	5–10
Intracranial tumours	5
Normal pressure hydrocephalus	6
Huntington chorea	3
Chronic drug intoxications	3
Miscellaneous diseases (hepatic failure, pernicious anemia; hypo- or hyperthyroidism; dementias with Parkinson disease, amyotrophic lateral sclerosis, cerebellar atrophy; neurosyphilis; Cushing syndrome, Creutzfeldt–Jakob disease, multiple sclerosis, epilepsy)	7–10
Undiagnosed types	3
Pseudodementias (depression, hypomania, schizophrenia, hysteria, undiagnosed)	7

Reprinted from Wells[7].

Table 3. A clinical classification of 53 Indian cases of dementia

Primary:	
Pre-senile	4
Senile	4
Secondary:	
Arteriosclerotic	6
Neurosyphilis	9
Encephalitis	4
Neoplastic	9
Demyelinating:	
Progressive degenerative brain disease in children	9
Schilder's	2
Lipidosis	1
Metabolic, endocrine and deficiency:	
Myxoedema	3
Alcoholic	2
Total	53

Reprinted from Bharucha *et al.*[1]

Table 4. Clinical and/or pathological diagnosis in 20 Indian cases of dementia

Diagnosis		No. of cases
Arteriosclerotic dementia		9
(a) Generalized cerebral arteriosclerosis	7	
(i) Binswanger's disease?	1	
(b) Middle cerebral artery occlusion	2	
General paralysis of the insane		3
Intracranial tumours		2
Alzheimer's disease		2
Cerebral venous thrombosis		1
Pellagra		1
Subdural haematoma		1
Ischaemic leucoencephalopathy		1
Total		20

Reprinted from Mani and Kishore[2].

Table 5. Clinical types of dementing illnesses in an Indian population ($n=40$)

	n	%
Alzheimer's disease	4	10.0
General paresis	3	7.5
Senile dementia	5	12.5
Multiinfarct dementia	2	5.0
Normal pressure hydrocephalus	2	5.0
Huntington's chorea	1	2.5
Progressive supra-nuclear palsy	1	2.5
Type unknown	22	55.0

Reprinted from Kalyanasundaram *et al.*[3]

Table 6. Diagnostic categories of dementia in a population of Indian patients

	Clinical ($n=60$)	Pathological ($n=10$)
Multiinfarct	9	2
General paresis of insane	5	2
Normal pressure Hydrocephalus	4	–
Pre-senile dementia 40–59 years	16	1 (ceroid lipofuscinosis)
		1 (multiinfarct dementia)
		1
Senile dementia 60 years and above	21	(multiinfarct dementia)
		1
Type unknown less than 40 years	5	(Hallervorden–Spatz disease)
		1 (ceroid lipofuscinosis)
		1 (no definite pathology)

Reprinted from Srinivas *et al.*[4]

in a related publication from the same group[8]. As computed tomography (CT) or magnetic resonance (MR) scanning were not available then in our country, all the reports suffer from absence of access to the great information provided by sophisticated imaging, which can reveal parenchymatous diseases like leukodystrophy, lacunar and other infarcts, small tumours, degenerative changes, demyelination, inflammatory reaction, etc. not seen through the older pneumoencephalography and angiography. This lacuna has now been filled in most of the major neurological centres of the country, and if a more sophisticated neurochemical laboratory support was forthcoming, it would not be difficult to thoroughly reappraise the considerable problem of dementia and dementing illness in India by a combined clinicopathological, radiological, neurochemical approach.

Differential diagnosis

As mentioned earlier, it seems appropriate to move agewise upwards in discussing the differential diagnosis of dementing illnesses, to use a classification based upon chronological age, with the full realization that quite a few of these will transgress such age barriers. We shall also stress the available published Indian data.

Age 1 to 15 years

It has not been easy to specifically identify a whole range of progressively dementing disorders in the first decade or decade and a half of life in India for want of modern laboratory facilities. Laboratory medicine provides growing opportunities for diagnostic support. This has limited the possibility of diagnosis during life to only those disorders where there are obvious extracranial or other neurological features indicating the disease, or where simpler laboratory tests or imaging are required, like those for tuberosclerosis, Wilson's disease, GM2 gangliosidosis, mucopolysaccharidosis, Hartnup's disease, Lafora body disease, leukodystrophies, etc. All these have been seen in India and some have been well reported.

Leukodystrophies. With the advent of CT and MRI, cases of adreno, metachromatic and megalencephalic leukodystrophy have been increasingly identified though not always proven by laboratory tests. Murthy *et al.*[9] reported seven cases of metachromatic leukodystrophy in children and one adult, proven by demonstration of metachromasia on cresyl violet and toluidine blue staining of biopsied sural nerve.

Classical changes in the white matter by CT scan had initially indicated the diagnosis though it was not possible to demonstrate reduced activity of the enzyme arylsulphatase A in the urine or in the white cells. Incidentally, Austin's story[10] of the discovery of deficiency of arylsulphatase A as the cause of metachromatic leukodystrophy makes fascinating reading, especially as the research was done in close collaboration with an Indian scientist (Bachhawat, in Vellore). Singhal *et al.*[11] reporting 18 patients with leukodystrophy and megalencephaly claimed that this was the commonest leukodystrophy seen by them in the Indian population. The median age at onset was 16 months and their patients presented with delayed motor and mental milestones and pyramidal and cerebellar signs. The course of the disease was relatively 'benign' and one of their patients was alive at the age of 19 years. No biochemical work-up was done. Sridharan *et al.*[12] have reported a family of adrenoleukodystrophy recently. X-linked inheritance, adrenocortical insufficiency (Addison's disease), clinical features and classical CT appearances left no doubt about the diagnosis, though laboratory confirmation could not be done. I have looked after a young man with Addison's disease, progressive dementia, myeloneuropathy and classical CT and MRI changes (Figure 1) of adrenoleukodystrophy in whose plasma high levels of long chain fatty acids were found, confirming the diagnosis.

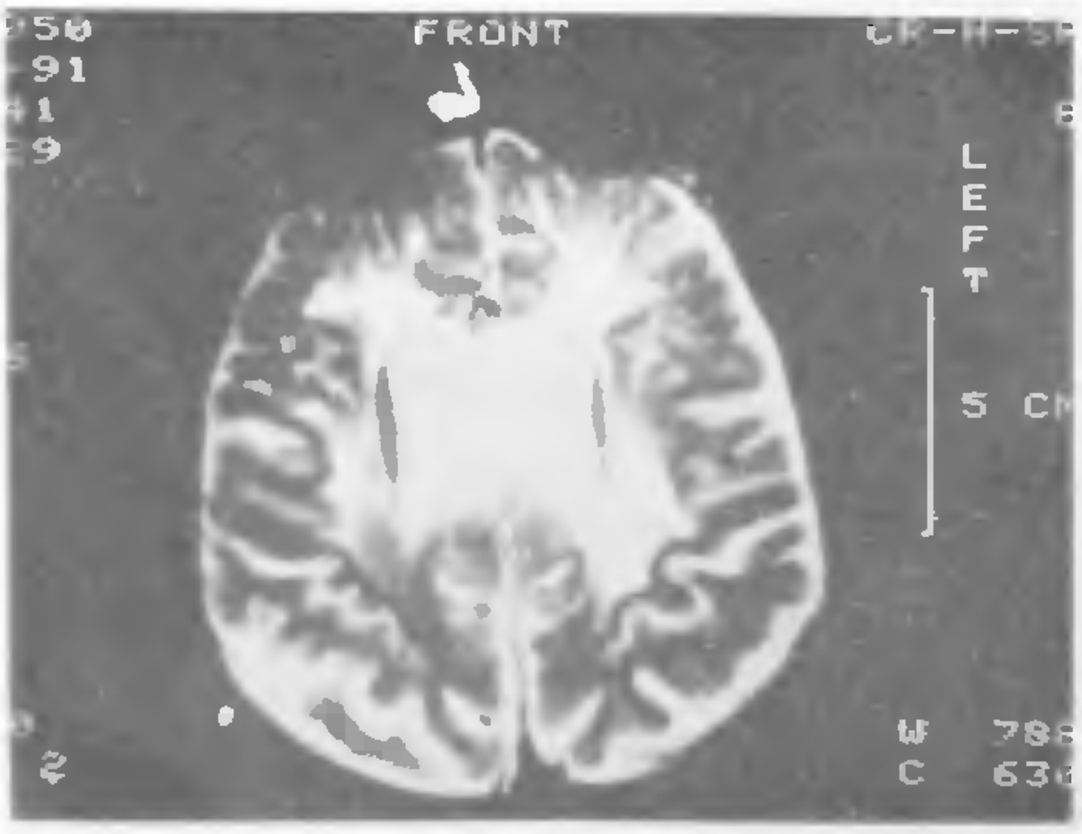

Figure 1. A T_2 W axial MRI scan of the brain of a young adult with adrenoleukodystrophy. Note classical, bilateral, periventricular, white-matter, hypertense lesions, a little more obvious posteriorly.

Wilson's disease. The first case of biochemically proven Wilson's disease noted in India was diagnosed by me; the patient was a 9-year-old boy belonging to a sibship of 8 children, 5 of whom were ultimately found to be affected. Subsequently, children from three other families were identified with the same disease and a report was made[13]. In all of them, dementia formed a prominent feature, along with a variety of involuntary movements. Later reports of larger numbers from the same group[14,15] showed that the age at onset of the disease was between 5 and 20 years in all except two patients. Mental changes usually presented with failing performance in school (8 out of 12 children). Patients presenting with hepatic failure or renal osteodystrophy were also included in the series.

Two recent reports are also relevant here. Swamy *et al.*[16] (Bangalore), reporting the largest Indian series to date (108 patients in 99 families), mentioned that 38.6% of their patients were mentally retarded and 8.9% had psychiatric symptoms, whilst Ghosh *et al.*[17] (Calcutta) found dementia and behavioural abnormalities as common psychiatric manifestations. The tell-tale Kayser–Fleischer rings were consistently present in all the series, making the clinical diagnosis easy. The onset in childhood, autosomal recessive heredity, the Kayser–Fleischer rings, Parkinsonism features, involuntary movements, mental retardation, seizures and other lesser signs, along with hepatic disorders in some of the primarily neurological cases, leave not much doubt about the clinical diagnosis. The laboratory investigations are merely confirmatory. However, diagnosis can be missed in an atypical purely neurological case, as for example that of an adult with only progressive dementia without a positive family history, where the Kayser–Fleischer rings are not seen by the naked eye and slit lamp examination is not requested.

Lafora body disease. Satishchandra *et al.* (personal communication, 1991) have recently written that they have seen a large number (21) of pathologically proven cases of Lafora body disease, including some familial types, at the National Institute of Mental Health and Neurosciences (NIMHANS) and claimed that theirs is the second largest series in the world.

Subacute sclerosing panencephalitis (SSPE). This was first identified by Dawson[18] in 1933 and has all but disappeared from the Western world with the control of measles through early vaccination programmes. It was once believed that SSPE was not common in India[19], although two case reports had already appeared[20,21]. However, it was subsequently found that children and occasionally young adults with this invariably fatal disease appeared with monotonous frequency in every paediatric and neurology department of our country, and a large number of rural and semi-urban patients

must have died unattended. Such patients, which I have also seen in good numbers, but not reported, present usually between the ages of 8 and 12 years with a subacutely progressive dementia, preceded, accompanied or followed by myoclonic jerks. The child over a variable period of time, usually weeks to months, becomes mute and bedridden, with tremors, choreoathetosis, rigidity and pyramidal signs. Less frequently, cerebellar signs, nystagmus, and a variety of visual disorders like cortical blindness, optic pallor, maculopathy, papilloedema and choroidoretinitis are seen. The clinical picture is fairly classical even at onset and not difficult to diagnosis even without the often specific electroencephalographic (EEG) abnormality of periodic complexes (Figure 2).

After Mani *et al.*[22] published a report of four cases in 1964, a large series[23] of 39 cases appeared in 1974 with EEG findings, measles antibody titre estimations, and, most importantly, postmortem confirmation in 15 cases[24]. None of the patients were immunized against measles. They maintained that the disease was as common as earlier reported from the West. In a recent update of that series, Singhal with other colleagues[25] has reviewed the collective data of 193 patients (including the 39 cases mentioned above) seen in the Departments of Neurology of the J. J. Group of Hospitals and the Bombay Hospital over 28 years (1962–1990). The mean age at onset was 10.5 years and males (151) predominated. No clustering, regional or racial predilection was found. Thakare *et al.*[26] have also reported 23 cases from Pune. Proceedings of a recent symposium on SSPE held in Vellore[27] and a publication by Khwaja *et al.*[28] also contain much updated information regarding this disease in India. It appears that an epidemiological survey and an aggressive immunization programme against measles to stamp out this disease which takes the lives of so many Indian children annually is overdue.

Brain tumours (intracranial space occupying lesions) and chronic hydrocephalus. Brain tumours (intracranial space occupying lesions) are a frequent cause of neurological illness amongst Indian children. Amongst these tuberculomas are the commonest, though happily their numbers are diminishing. Yet it is rare to see a child presenting with dementia from the direct effect of a space occupying lesion even if it is in the region of the frontal lobes. What is more common is the child with a chronic slowly increasing hydrocephalus who presents primarily with progressive mental retardation amounting to dementia without headache, vomiting or papilloedema. The example of a child with slowly failing performance at school due to aqueduct stenosis is well known (Figure 3); fortunately, the rather large head indicates the diagnosis to the discerning, though in late childhood the tell-tale 'crackpot note' may be missing. Some of these children are misdiagnosed as being mentally retarded and sent to a special school, a bad mistake still being made, even where a CT scan facility is available. A plain radiograph of the skull can also be quite revealing by showing changes due to raised intracranial pressure.

Chronic hydrocephalus and 'creeping' dementia can also be seen as delayed sequelae of a fully healed tuberculous basal meningitis. Relatively slow-growing midline or posterior fossa tumours can do the same, though perhaps less frequently.

Age 16 to 55 years

Some of the diseases of childhood discussed earlier will overflow into this group, but will not be mentioned here except for brain tumours and hydrocephalus both of which need special mention.

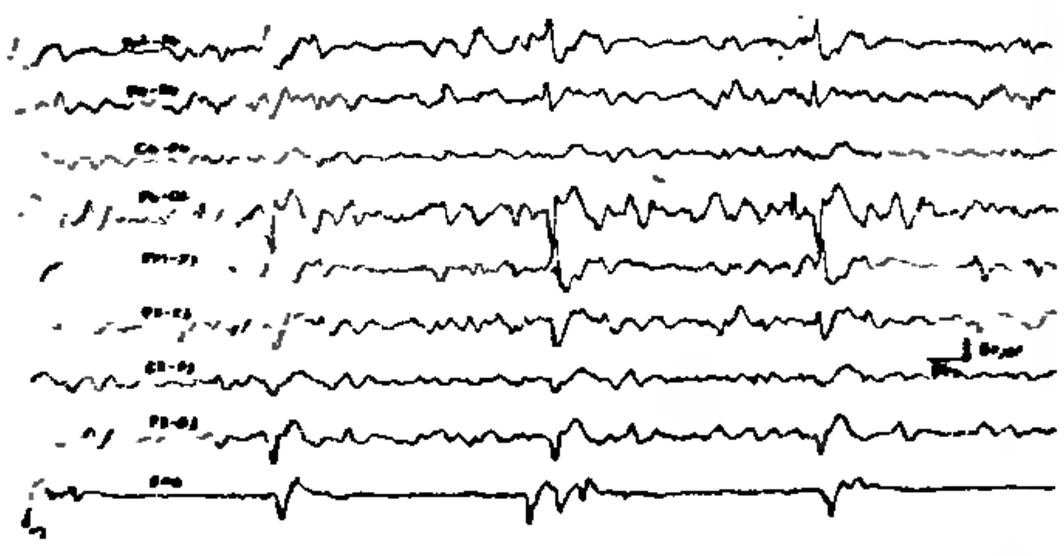

Figure 2. EEG of a 9-year-old girl, with subacute sclerosing panencephalitis showing repetitive, stereotypic, periodic complexes associated with myoclonic jerks (recorded on channel 10)

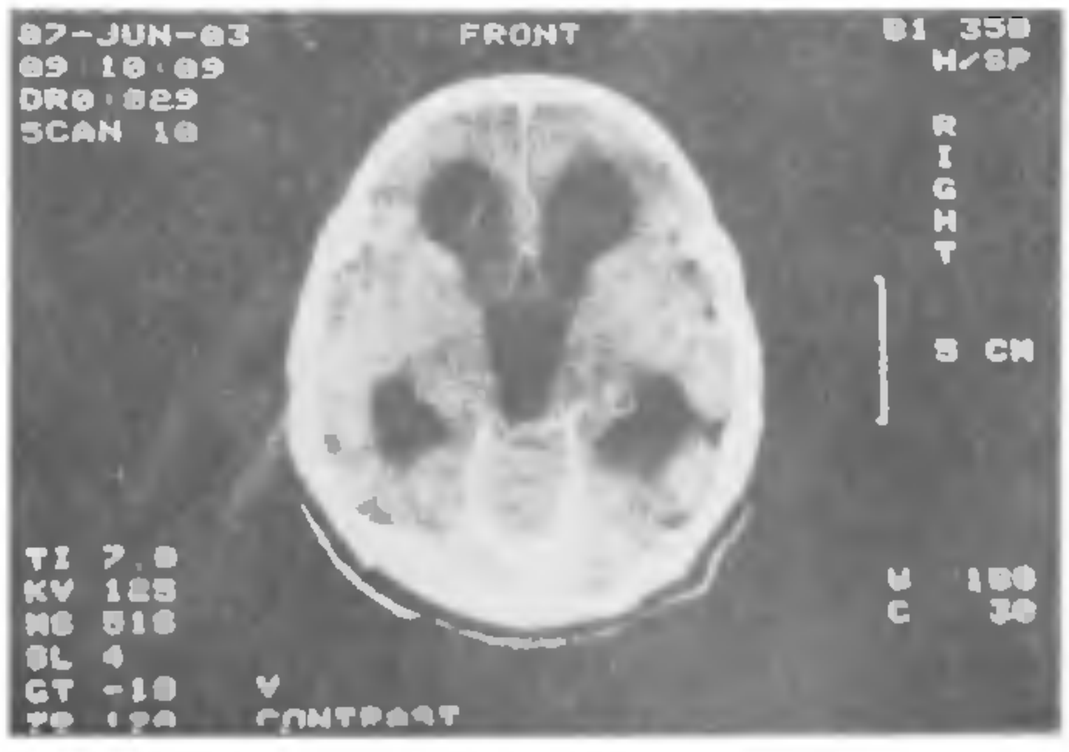

Figure 3. Axial CT scan of the brain of a girl aged 18 years with progressive mental deterioration showing marked hydrocephalic dilatation of the lateral and third ventricles. The latter is tapering posteriorly to a point where there was aqueduct stenosis, not seen here. The cortical sulci are effaced

Brain tumours and hydrocephalus (chronic and normal pressure) Unlike children, adults with benign or malignant tumours in the region of the frontal lobes or corpus callosum frequently present with dementia (Figure 4), and such patients are seen as often in India as elsewhere. On the other hand, in my experience, patients with tuberculoma, whose numbers amongst adults are also diminishing, rarely present with dementia. Most come with seizures and hemiparesis even when the lesions are in the frontal lobe.

It is not always realized that even amongst adults benign mid-line and posterior fossa tumours, such as colloid cysts, acoustic neuromas and meningiomas, as well as aqueduct stenosis, can manifest as dementia. Shephard and Wadia[29] were the first to point out that acoustic neuromas can masquerade behind a presenting symptom of progressive dementia without signs or symptoms of raised intracranial pressure, a fact not known to the great Cushing and not mentioned in his landmark monograph on this subject. A short shuffling gait, as seen with normal pressure hydrocephalus (discussed later), may also be seen and can simulate the gait disturbances of Parkinson's disease. A recent article from India by Srivastava and Narayana Reddy[30] mentions that 12.8% of 108 patients with acoustic neurinoma had predominant psychiatric symptoms.

In the same group can be included patients with normal pressure hydrocephalus who present with gait disorder, sphincter incontinence, falling attacks and eventually dementia. The patient usually does not complain of headaches and there are no obvious manifestations of raised intracranial pressure. Beginning with imbalance and hesitancy, the gait disorder worsens to a festinate shuffling gait. Incontinence often develops early, but obvious mental changes usually follow after some delay. Previous subarachnoid haemorrhage, meningitis and trauma have been known to cause this syndrome, but often the cause is not found. The majority of patients are in older age groups (see below). In such elderly subjects the condition is often mistaken for multiinfarct dementia or a primary degenerative disorder, such as Alzheimer's disease or Parkinson's disease with dementia. As a ventriculo-peritoneal or theco-peritoneal shunt can relieve the symptoms, the differential diagnosis is very important and is usually completed by CT or MR scans which shows dilated ventricles without convolutional atrophy. Radionucleide cisternography may show ventricular reflux and delayed diffusion over the cerebral hemispheres. Removal of a large amount of cerebrospinal fluid can result in dramatic improvement, serving as a useful and simple diagnostic test. Shunt surgery has sometimes been unsuccessful because cases may be badly selected, including those deviating from the classical syndrome. Patients with dementia without gait disorder, or with aphasia, apraxia or focal neurological signs should not be recommended for shunt surgery, as they indicate alternate or additional conditions such as those mentioned above.

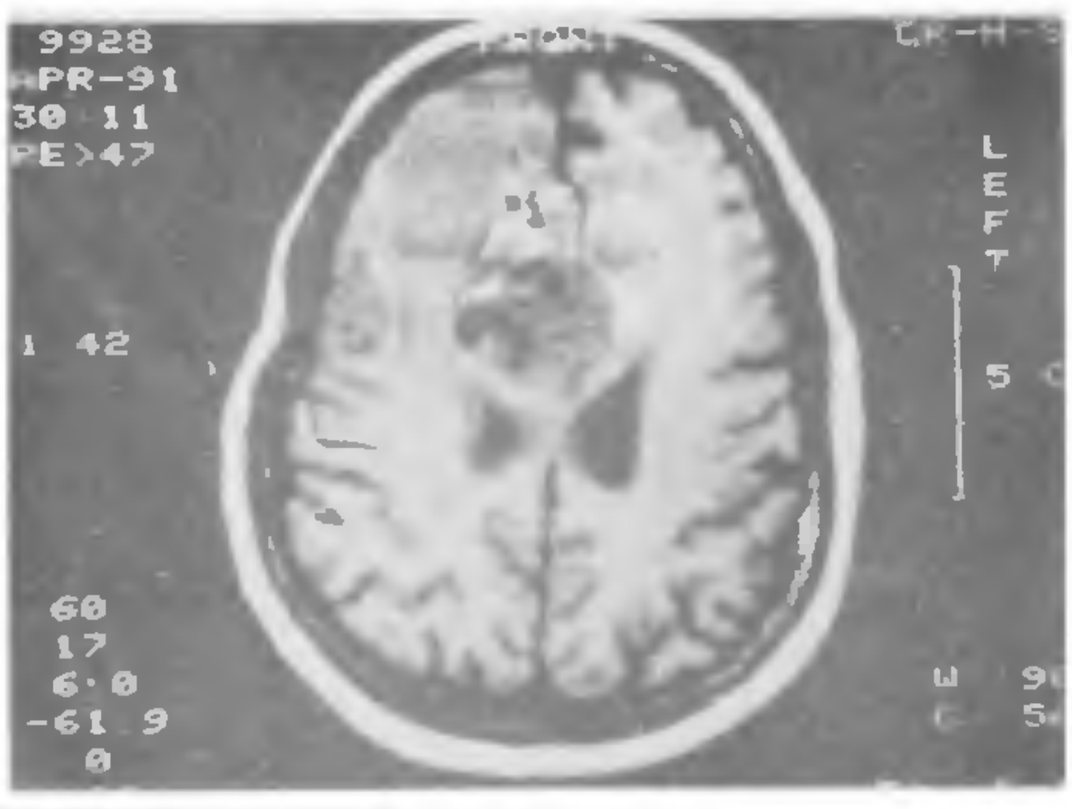

Figure 4. T_1W_1 gadolineum-enhanced, axial MR scan of brain showing a large corpus collosal glioma with bifrontal extension, more to the right

Infections

Neurosyphilis. This is on the wane in most parts of India. I have not seen a single patient with general paralysis of the insane (GPI) in two decades. Earlier reports, however, attest to its continuing presence in India at least through the seventies, as evidenced by reviews of 240 cases of GPI from NIMHANS, Bangalore[31] and of 132 patients with neurosyphilis[32] from Madurai. As expected, dementia was a prominent feature. Venkoba Rao *et al.*[33], recounting their experience of 'general paresis in the psychiatric department of a general hospital in India,' mention that simple dementia occurred in 55.9% of patients with neurosyphilis. Srinivas and Shankar[34] mention that neurosyphilis accounted for 7.5 to 17% of patients who presented with dementia amongst the various series they reviewed in their appraisal of dementia in India.

Cysticercosis. Cysticercosis is rampant in India and dementia is one of its main symptoms, although less common than seizures. The meningitic and parenchymatous varieties both cause dementia. In the latter variety, which is more commonly seen in India, multiple cysticerci in all stages of evolution enter the brain, causing seizures, dementia, visual disorders, paralysis and raised intracranial pressure. Wadia *et al.*[35] have described an extreme form of this, where thousands of living cysticerci invade the body causing pseudohypertrophy of muscles simulating muscular dystrophy, dementia and intractable epilepsy (Figure 5). Localizing and obvious signs of raised pressure were minimal.

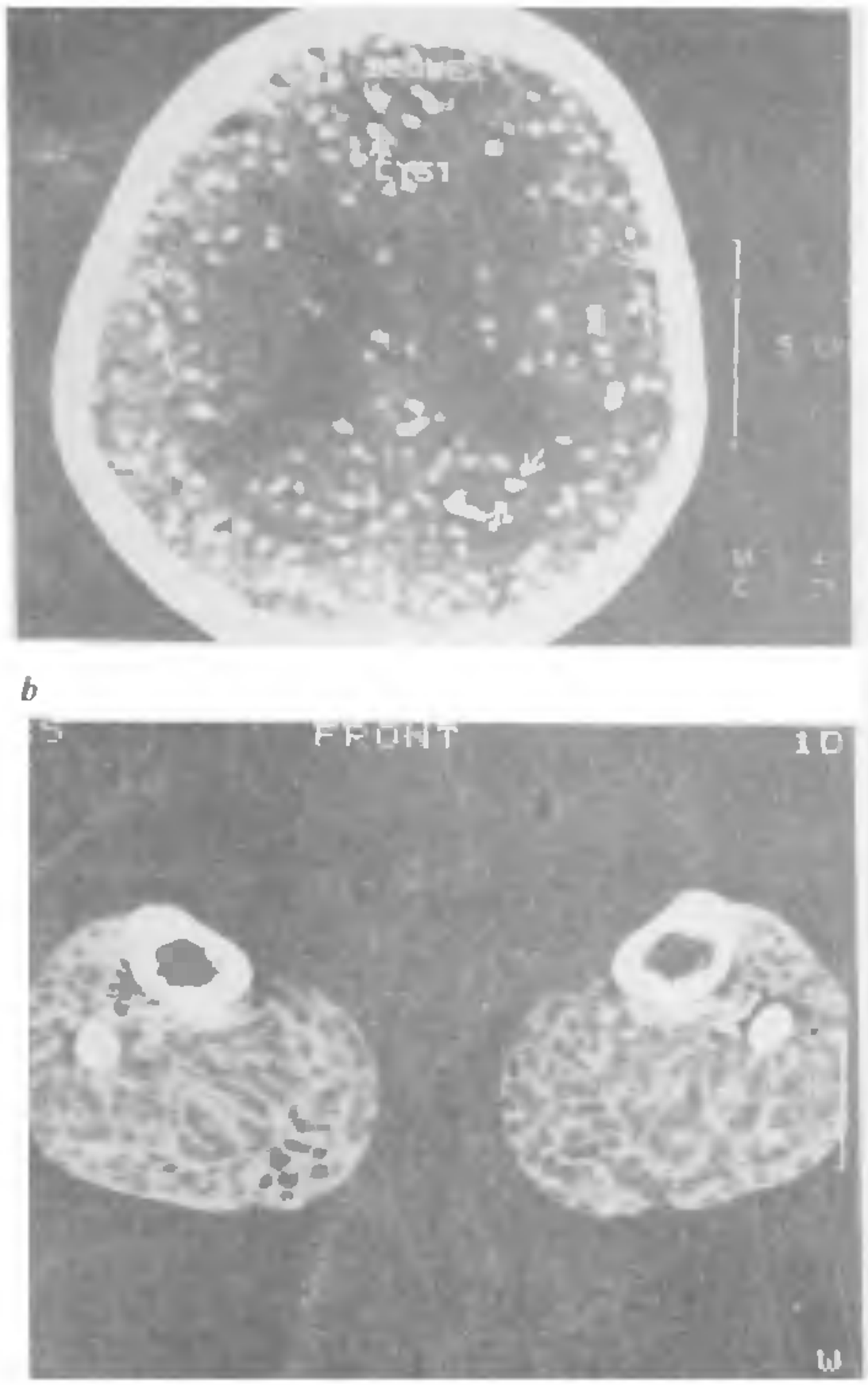

Figure 5. **a**, A pre-contrast slightly magnified axial CT scan of the brain of a young girl showing an enormous number of living cysticerci even in this one plane. The arrows point to the scolax and cyst. ***b***, Unenhanced CT scan of calf muscles in which a vast number of living cysticerci are lodged. The scolices are the white dots in the more obvious cysts. They were better appreciated on enlargement.

They have referred to the earlier literature and mentioned that though this extreme form is rare, most of the published cases have been amongst Indians (18) and Chinese (13). Surprisingly only one such case was reported from South America (Brazil), where cysticercosis is widespread.

Creutzfeldt Jakob disease This well-recognized novel infectious disease ('prion' disease) is seen all over India, and should always be considered in the differential diagnosis of dementia in a patient above the age of 40 years. The disease is transmissible via tissue transplantation. The pathology is that of a spongiform encephalopathy. The dementia, usually rapidly progressive with all the higher mental faculties simultaneously impaired, is accompanied by or followed by myoclonic jerks, pyramidal, extrapyramidal and cerebellar signs and visual disorder in different combinations. The electroencephalographic changes are fairly classical, with slowing of the background activity and periodic complexes (Figure 6), so that a confident diagnosis can be made during life. No survivors have been reported from anywhere in the world.

The disease has been seen all over India. The first case reported by Rao and Sailapathy[36] in 1965 lacked autopsy confirmation, but Roy *et al.*[37] soon followed with a report of an autopsy-proven case in which virus-like particles were demonstrated by electron microscopy. Subsequently, case reports were published by Gupta *et al.*[38], Soma Sundaram and Menon[39], Singhal and Dastur[40], and Srinivas *et al.*[41]. In 1988, Shankar and Satishchandra[42] attempted to compile a registry of cases seen in India through a questionnaire and were able to collect 23 sufficiently well-documented cases over the previous 18 years. Seventeen of these were histopathologically proven and in the others EEG confirmation was available, classifying these as probable cases. Not all cases had been previously published. Eleven patients were from Bombay, six from Bangalore, two each from Madras and New Delhi, and one each from Madurai and Vellore, pointing to its general prevalence, without evidence of geographical clustering. The predominance of cases from Bombay and Bangalore merely attested to a greater interest in the study of this disease, and to higher autopsy rates as well as other factors. The authors rightly mentioned that the real prevalence must be considerably greater, which is understandable as access to neurologists and neurological centres with an EEG facility is available in

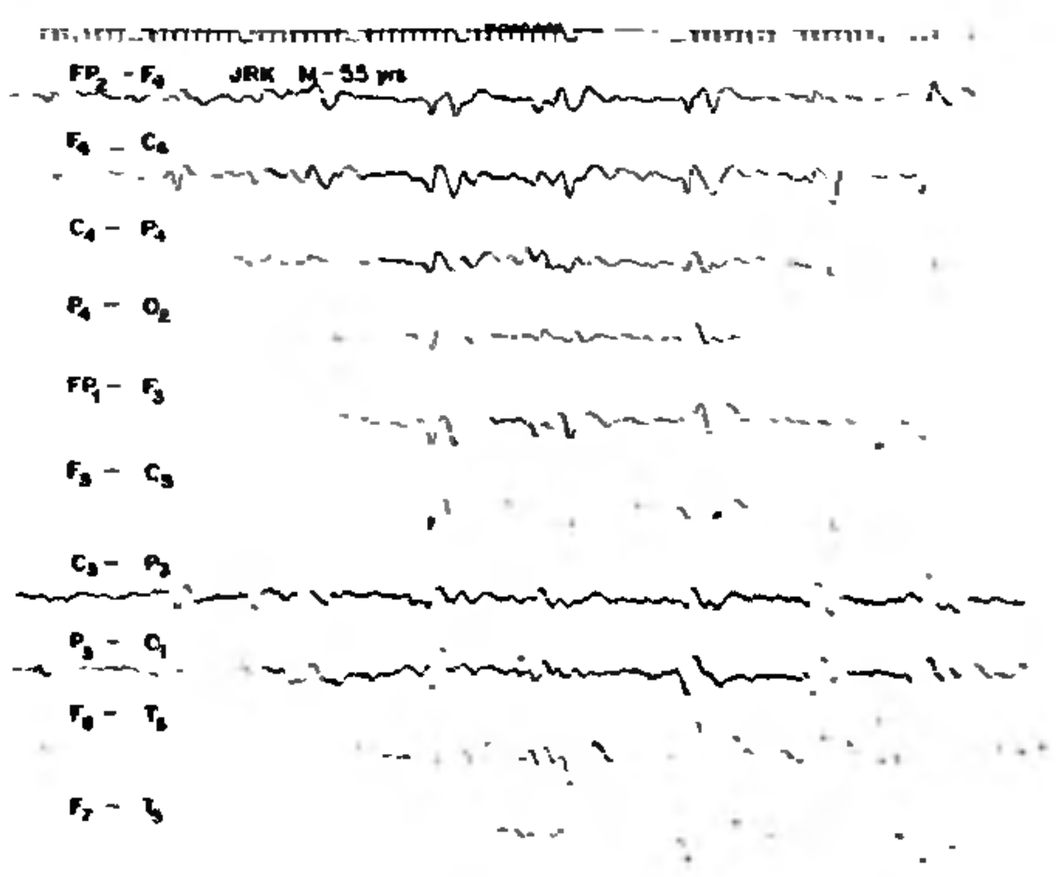

Figure 6. Characteristic EEG of a man of 55 years with Creutzfeldt Jakob disease. Note the bilateral, synchronous, periodic complexes

only a few localities, mostly in major cities, the vast hinterland remaining unattended.

The lack of satisfactory documentation also has precluded entry of additional cases into the registry. I have personally seen six cases in a 35-year practice in Bombay which could not be offered for the registry, as the case histories or EEG were scattered in different hospitals and not easily available. After the registry closed, Dastur *et al.*[43] added two more cases and pathologically analysed their data of six brains. Satishchandra and Shankar[44], updating their registry to the year 1990 (20 definite, 10 probable cases), mentioned that their study did not reveal novel types of clinical information or other data. The findings were generally consistent with those in the world literature. Dementia affected all 30 patients, followed by myoclonus in 27, pyramidal signs in 27, extrapyramidal signs in 24, cerebellar in 11, and anterior horn cells in 8. Complaints of seizures (11), visual (10) and psychiatric (3) disturbances were also made. In my own patients, visual disorder, bordering on cortical blindness, has been quite predominant.

AIDS encephalopathy. Symptomatic AIDS is being increasingly seen in India. By October 1988, 25 patients had been reported[45] of which 16 were Indians. Neurological patients present with chronic tuberculous or fungal meningitis along with other manifestations of AIDS, but there were some in whom a subcortical progressive dementia predominated. We[46] have reported the first such case from India. He was a man of 56 years, who had previously received a blood transfusion. He came with weight loss, fever, diarrhoea, pulmonary tuberculosis, oral and oesophageal candidiasis, and progressive dementia. An occult carcinoma was entertained as part of the differential diagnosis of dementia, but this was excluded and the diagnosis of AIDS confirmed by various laboratory tests. A very similar case was later reported in 1990 by Srinivas[47].

Metabolic and toxic causes. Only a few comments need to be made.

Vitamin B_{12} deficiency. It is well known that dementia can be the dominant feature of vitamin B_{12} deficiency in rare cases. This has been observed in cases seen in India[48], where vitamin B_{12} deficiency mostly occurs through overt or covert malabsorption of the vitamin, especially if there is additional malnutrition, as in imbalanced vegetarianism[48-50]. Addisonian pernicious anemia is known to be rare amongst Indians. Random examinations of the sera of normal vegetarians in India have shown significantly lower levels of vitamin B_{12} than in the sera of non-vegetarian controls[51-53].

Pellagra. There was a time when pellagrous dementia was endemic in certain parts of India reaching 'epidemic' proportions when famine prevailed. In 1969, Gopalan[54] had stated that 'in Hyderabad 1% of admissions to general hospitals and (in certain seasons) 8-10% of admissions to mental hospital are cases of pellagra.' A similar situation was seen in Rajasthan[55, 56]. The dementia was either mild and chronic[57] or took the form of an acute 'madness', especially during epidemics. Diarrhoea and classic pellagrous dermatitis were often present, but peripheral neuropathy, myelopathy and even amblyopia have been mentioned. It was uncertain if these cases were related to the lack of nicotinic acid alone or to an associated deficiency. There is no difficulty in diagnosis, especially as the signs vanish with a single injection of niacin. Happily, those days are in the past. Mild pellagrous dementia is now occasionally seen in urban pellagrous alcoholics[58].

Korsakoff's psychosis and alcoholic dementia. Korsakoff's psychosis refers to a disorder in which retentive memory is impaired out of proportion to deficiencies in other cognitive functions. Commonly associated with malnourished alcoholics, it can also result from other disorders. It is interesting that, whereas thiamine (vitamin B_1) deficiency is believed to be the cause among the malnourished alcoholics in the West (especially in the US), Wadia[58, 59] has pointed out that it is rarely seen amongst the chronically malnourished in India. He hypothesized that 'continuing chronic deprivation seems to affect the nervous system in a different way than malnutrition reported in Western alcoholics[59].

Alcoholic dementia occurs in chronic alcoholics of India, as is the case elsewhere. Although no data are available, it is fair to assume that the prevalence is greater among groups of people or tribes in which alcoholism is common.

Manganese poisoning. India has one of the world's richest manganese ore deposits. Cases of manganese poisoning have been reported[60-62] well in the past but no new cases have been seen since. Wadia[63] made a detailed study of 11 patients at the J. J. Group of Hospitals. These were selected from among a group of 28 examined at site in the mines. Progressive dementia was not an outstanding symptom, though a few exhibited short or long periods of acute mania with irrelevant talk, restlessness and even violence. The classical picture mainly comprised Parkinsonism, abnormal postural reflexes, a tendency to walk on toes (cock-walk), sham mirth or pathological laughter and, at times, unprovoked weeping.

Degenerative diseases

Huntington's disease is believed to be relatively rare in India, but a report made by Argikar *et al.*[64] from our

department of neurology at the J. J. Group of Hospitals and the Bombay Hospital described the clinical features of 26 'classical' cases from 26 families seen in Bombay from 1963 to 1976. The patients hailed from all parts of India, having come to the cosmopolitan city of Bombay for various reasons. The cases were seen in all three major communities of India: Hindus, Muslims and Christians. No Jewish family was identified, although this may be because their numbers had drastically dwindled following the independence of India and the establishment of the Jewish State of Israel. Earlier reports of 12 families[65, 66] and 4 families[67] from the Punjab and 10 families from Bombay[68] attest to the not uncommon occurrence of this disease in India. It is interesting that only one case has been reported from NIMHANS, which is associated with a large mental hospital and neuroscience centre (Table 5)[3]

Parkinson's disease. Dementia in a proportion of patients with Parkinson's disease is well recognized. The probable prevalence is between 15 and 20%. Nagaraja *et al.*[69] mentioned that 28 of their 48 patients (58%) showed deficits on neuropsychological testing, but in 19 there was definite evidence of a cortical type of dementia with cognitive difficulty. The peak incidence was the sixth decade, though seen at all ages. The deficit was seen equally in mildly and severely disabled patients, and the severity did not correlate with the physical disability.

Steele, Richardson, Olzewski disease (progressive supranuclear palsy). Dementia in this disease is typically of the subcortical variety with memory impairment being more apparent than real. Frontal lobe deficits are prominent, along with other features such as bilateral grasp reflexes. There is little cognitive impairment and no obvious cortical atrophy on imaging. Dementia may not be striking in comparison with trunkal dystonia, Parkinsonian features, vertical gaze palsy, pseudobulbar palsy and pyramidal signs.

I have seen nearly a dozen patients with this disease in India, but never published a report. Jayakumar *et al.*[70] studied eight patients in detail, both clinically and by imaging. They found evidence of dementia in five, 3 of the subcortical and 2 of cortical type. The CT scan revealed midbrain, pontine and subcortical atrophy.

Trauma

Subdural haematoma. Patients with chronic bilateral subdural haematoma can present with progressive dementia. A history of trauma may not be forthcoming even after careful questioning which is often not done. The result is that an eminently curable disease is missed. Routine CT and MR imaging have appreciably reduced this margin of error, often showing the haematomata to a surprised clinician who had expected to see evidence of Alzheimer's disease or multiinfarct dementia. In earlier days this misdiagnosis was relatively common.

Dementia pugilistica. This condition, though known earlier, is being increasingly recognized and commented upon even in the lay press. Dhamija *et al.*[71] studied 14 amateur Indian army boxers (in India boxing is not a professional sport, if it can be called a sport) and found that four had a combination of mood changes, forgetfulness, low IQ, slurred speech, ataxia, tremors and cerebellar and pyramidal signs. They did not mention Parkinsonism, which is reportedly a common manifestation. They mentioned that the patients had boxed on average for 3 to 4 months a year for 10 years, and that the symptoms appeared as early as after 6 years of boxing or as late as after 17 years.

Intracranial vasculitis, microangiopathy, and dementia as a presenting symptom of occult carcinoma. These conditions have all been seen, though no reports have been published from India.

Age 56 years and above

In this age group are included Alzheimer's disease, Pick's disease, multiinfarct dementia and Binswanger's subcortical arteriosclerotic encephalopathy. Together they form by far the largest group, accounting for over 60% of all patients with dementia. Their numbers are fast increasing, as a result of the increase in the number of the aged all over the world, so much so that Alzheimer's disease is believed to have reached 'epidemic' proportions in the US.

Alzheimer's disease. There is voluminous literature on all aspects of Alzheimer's disease, some of which is referred to by others in this issue. I can only mention a few locally relevant observations here.

Shankar *et al.*[8] stress the 'absence of pathologically proven Alzheimer's disease' in their pathomorphological study of 10 Indian brains, hinting that Alzheimer's disease is less common amongst Indians. A glance at their table 1, however, shows the fallacy in this statement, as 6 of the 10 brains were from patients under the age of 45 years, when Alzheimer's disease is unlikely to occur; only two were above the age of 60 years, when the disease becomes more prevalent. Actually these two brains showed multiple infarctions, lesions that are also common in this age group.

Opinion amongst Indian clinicians, including myself, is that Alzheimer's disease is very much present, though age-related prevalence rates are not available to permit comparisons with the West. Srinivas and Shankar[34], quoting Nagaraja's unpublished study of dementia at

NIMHANS, mention that '30-38% of cases of dementia were in the group of senile and pre-senile dementia of Alzheimer type.' An instance of familial Alzheimer's disease, pathologically confirmed in the index patient, has now been reported from India[72]. In my own ageing community (Zoroastrian–Parsis and Iranis), in which the average age of survival has reached the seventies, Alzheimer's disease is quite frequently seen.

It appears that as longevity increases amongst Indians generally, the numbers of Alzheimer's disease patients will move up, as is already being seen in the financially and medically more privileged Indians.

Clinician diagnosis is not difficult in the classical case which begins with progressive memory loss, increasing intellectual impairment, language disorder, etc. It is not as easy to diagnose with less typical presentations, such as a predominant aphasia, agnosia, loss of topographical memory, or apraxia, when CT or MR imaging is required. Multiinfarct dementia, Parkinson's disease with dementia, bilateral subdural haematoma, normal pressure hydrocephalus, Binswanger's disease and pseudodementia, not uncommon with advancing age, enter the differential diagnosis. In some cases, a remarkable cortical atrophy with ventricular dilatation and absence of infarcts can be appreciated by good imaging (Figure 7), which can also distinguish the other conditions.

Multiinfarct dementia. This results from an accumulation of defects due to multiple, bilateral supratentorial infarcts. The predominant symptom is dementia and those with severe physical disability such as an acute severe hemiplegia, even if demented, are excluded from this group. Over some months or years small, focal, partly or wholly reversible episodes of neurological dysfunction, such as hemiparesis, aphasia, confusion, vertigo, dysarthria, or gait disorder recur followed by increasing defect of memory, intellect and other cognitive functions, resulting in dementia. The patient is slow physically and mentally. Pseudobulbar palsy, unstable or shuffling gait, pathological laughter or crying, incontinence, visuospatial disorientation, etc., are additionally seen in various combinations. The patients usually also have hypertension, diabetes, myocardial ischaemia, bouts of cardiac failure, and other manifestations of atherosclerosis.

Given the setting, clinical diagnosis is not difficult, but CT/MR imaging may be required to distinguish it from the other dementing disorders at this age (Figure 8). Jayakumar *et al.*[73] studied 30 patients with primary degenerative dementia (Alzheimer's disease and others) and multiinfarct dementia at NIMHANS with a view to differentiate the two disorders. They concluded that infarcts and white matter low attenuation lesions were the most distinguishing hallmarks of multiinfarct dementia, and that the various cortical and subcortical indices to measure cerebral atrophy were not as helpful.

The population at large in India is either unaware of the risks of hypertension, diabetes, obesity and other ravages of ageing, or is simply careless about taking regular treatments, suitable diets or exercises. Multiinfarct dementia is therefore common in our aged populations. Some believe that it is more prevalent than Alzheimer's disease, as the data in the tables published here seem to reflect.

Binswanger's disease. Also called subcortical arteriosclerotic encephalopathy, this condition was first described by Binswanger as a periventricular demyelinating disorder of the cerebral white matter in demented elderly hypertensive patients. Initially considered to be rare, it is now more commonly revealed

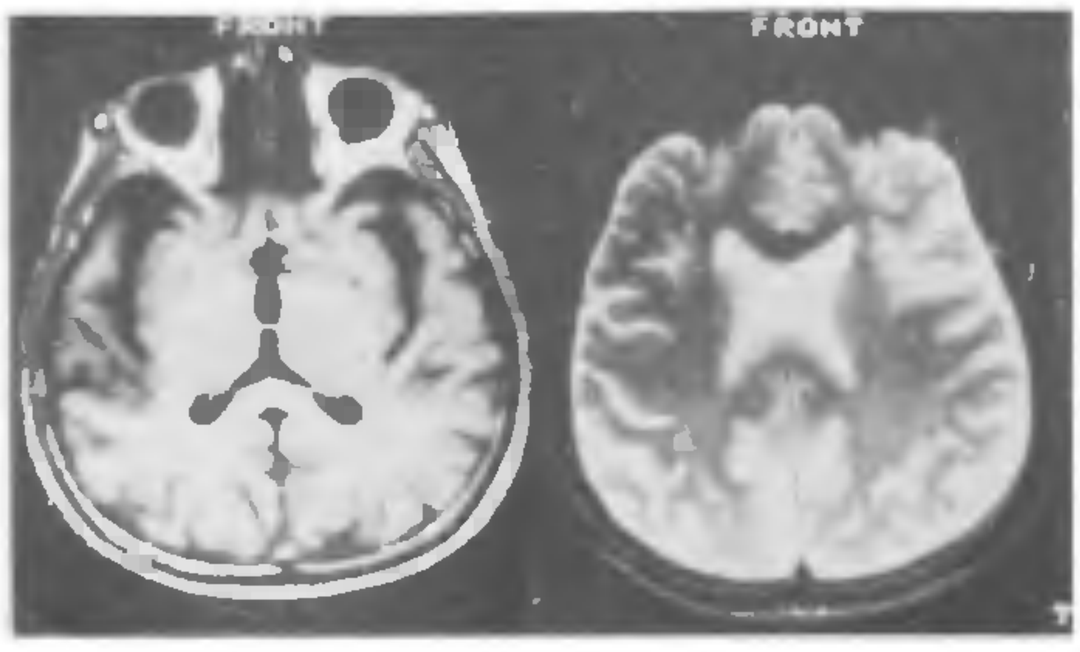

Figure 7. T_1W_1 axial brain MRI revealing marked dilatation of Sylvian cistern and cerebral cortical sulci of a patient with Alzheimer's disease (on the left). Another section (T_2W) shows marked cortical atrophy without much ventricular dilatation. No cerebral infarcts are seen (on the right).

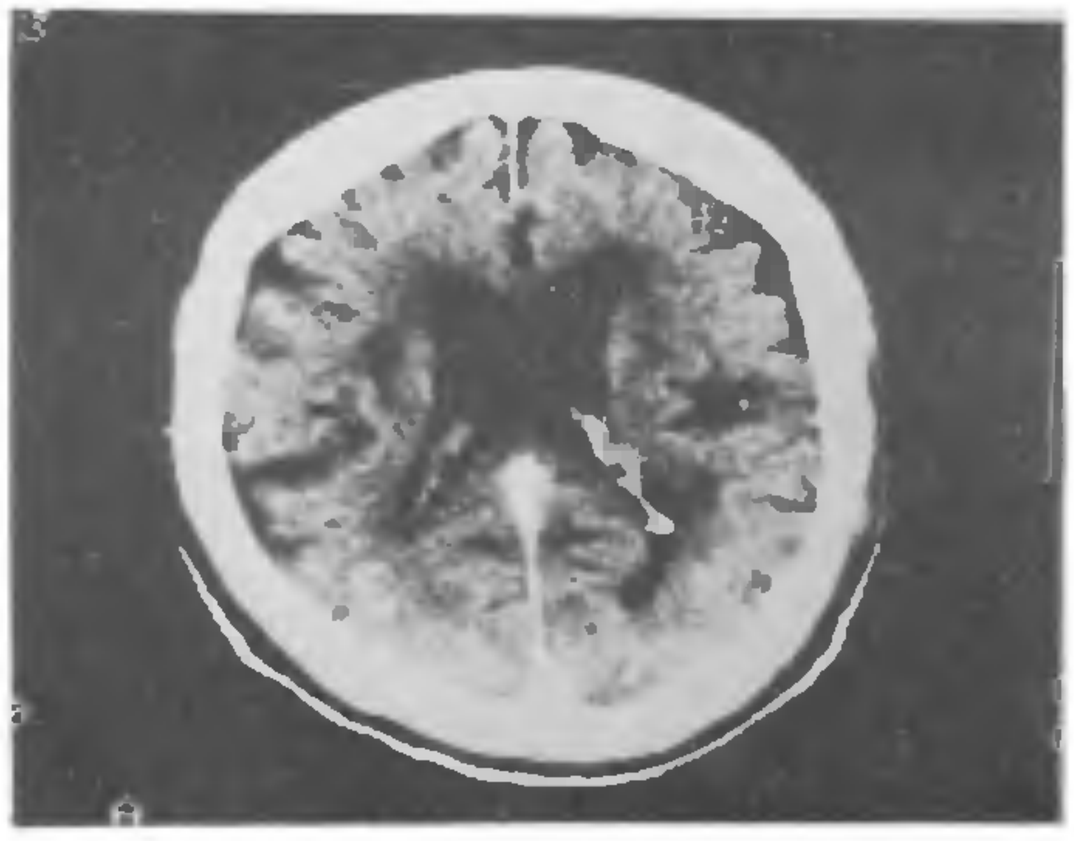

Figure 8. Axial brain CT scan of a man aged 70 years, showing bilateral periventricular deep white matter, low attenuation areas (infarcts) with mild dilatation of lateral ventricles and prominent cortical sulci.

by CT/MR imaging. Four cases, three pathologically proven, have been reported from NIMHANS over the years[2, 8, 74]. The clinical history may not be very different from multiinfarct dementia. Episodic events occur as often with demyelination as with infarction. Disinterest, memory loss, poor concentration, speech disorder and visuospatial and construtional errors are amongst the main symptoms. Motor signs with clumsiness, gait disorder, extensor plantar responses, released primitive reflexes and urinary incontinence are seen as the disease advances.

This condition is not easily differentiated from the other dementias of the aged, though hypertension is a constant marker. Periventricular demyelinating lesions, especially around the frontal and occipital horns, are seen by CT/MR imaging and are diagnostic in an appropriate clinical setting.

Conclusions

Patients with dementia and the many dementing illnesses at all ages require considerable attention from neurologists. With their numbers increasing, there is a greater need for more research globally, as so much about them is unknown. It is equally important for us in India to investigate independently and study dementias as it has considerable local, social and cultural implications.

1. Bharucha, E. P., Mondkar, V. P. and Seshia, S. S., *Neurol. India*, 1964, **12**, 80–93.
2. Mani, K. S. and Kishore, B., *Neurol. India*, 1964, **12**, 101–110.
3. Kalyanasundaram, S., Mahal, A. S. and Mani, K. S., *Indian J. Psychiatry*, 1979, **21**, 114–126.
4. Srinivas, H. V., Kalyanasundaram, S., Deshpande, D. H. and Vasundhara Devi, K., *Neurol. India*, 1982, **30**, 83–92.
5. Ramachandran, V., Sarada Menon, M. and Ramamurthy, B., *Indian J. Psychiatry*, 1981, **23**, 21-26.
6. Rao, A. V. and Madhavan, T., *Indian J. Psychiatry*, 1982, **24**, 258–267.
7. Wells, C., *Dementia*, Davis, Philadelphia, 1977, p. 250.
8. Shankar, S. K., Deshpande, D. H., Srinivas, H. V. and Kalyanasundaram, S., *Neurol. India*, 1982, **30**, 93-103.
9. Murthy, J. M. K., Sundaram, C., Anjaneyulu, A. and Meena, A. K., Metachromatic Leukodystrophy—*Clinical, Physiological* and MRI study in Abstract, 40th Annual Conference of the Neurological Society of India, 1991, p. 30.
10. Austin, J. H., *Chase, Chance and Creativity: The Lucky Art of Novelty*, Columbia University Press, New York, 1978, pp. 38 43.
11. Singhal, B. S., Gurusahani, R. D., Biniwale, A. A., Udani, V. P., Abstract, 40th Annual Conference of the Neurological Society of India, 1991, p. 30.
12. Sridharan, R., Harichand, U. and Lakshmi, P., *Neurol. India*, 1989, **37**, 606.
13. Wadia, N. H. and Dastur, D. K., *Neurol. India*, 1963, **11**, 1 18.
14. Dastur, D. K., Manghani, D. K. and Wadia, N. H., *Progress in Neurogenetics* (eds. Barbeau, A. and Brunette, J. R.), Excerpta Medica International Congress series no. 175, Excerpta Medica Foundation, Amsterdam, 1967, pp. 615 624.
15. Dastur, D. K., Manghani, D. K. and Wadia, N. H., *Neurol. India*, 1968, **18**, 21–31.
16. Swamy, H. S., Mazumdar, U. S. and Anisya, V., Abstract, 8th Asian and Oceanian Congress of Neurology, 1991, Abstract No. 0–04–10, p. 71.
17. Ghosh, P., Ganguly, C., Mukherjee, K. L., Patra, M. D. and Sen, S., Abstract, 8th Asian and Oceanian Congress of Neurology, 1991, Abstract No. 0–04–11, p. 71.
18. Dawson, J. R., *Am. J. Pathol.*, 1933, **9**, 7–15.
19. Annotation, *Lancet*, 1963, **1**, 153.
20. Desai, A. D. and Iyer, C. G. S., *J. Postgrad. Med.*, 1956, **2**, 153–162.
21. Mehta, B. C., Bagadia, V. N., Vardachari, K. S. and Vahia, N. S., *Indian J. Psychiatry*, 1959, **1**, 183–191.
22. Mani, K. S., Sriramachari, S. and Kishore, B., *Neurol India*, 1964, **12**, 42–49.
23. Singhal, B. S., Wadia, N. H., Vibhakar, B. B. and Dastur, D. K., *Neurol. India*, 1974, **22**, 87–94.
24. Dastur, D. K., *Neurol. India*, 1967, **15**, 51–69.
25. Singhal, B. S., Kini, G. N., Meshram, C. S. and Gurusahani, R. D., Abstract, Symposium on Neuroepidemiology, November, 1991, (Loosely distributed).
26. Thakare, J. P., Wadia, R. S., Deuskar, N. J., Sharma, V. Y., Kothari, S., Gore, N. M. and Ghosh, S. N., *Neurol. India*, 1987, **35**, 333–339.
27. *Subacute sclerosing panencephalitis–An update, Proceedings of* the Third International Symposium on SSPE, C. M. C., Vellore, October, 1989.
28. Khwaja, G. A., Gupta, M. and Sharma, D. K., *J. Assoc. Physicians India*, 1991, **39**, 928–933.
29. Shephard, R. H. and Wadia, N. H., *Brain*, 1956, **79**, 282–318.
30. Srivastava, V. K. and Narayana Reddy, G. N., *Neurol. India*, 1990, **38**, 277–284.
31. Narayanan, H. S., Narayana Reddy, G. N. and Rao, B. S. S., *Indian J. Psychiatry*, 1973, **15**, 374–377.
32. Srinivasan, K. and Ranganathan, P. G., *Neurol. India*, 1977, **25**, 19–25.
33. Rao, A. V., Ranganathan, P. S. and Natarajan, M., *Br. J. Psychiatry*, 1972, **121**, 143–146.
34. Srinivas, H. V. and Shankar, S. K., in *Progress in Clinical Neurosciences* (eds. Sinha, K. K. and Chandra, P.), Catholic Press, Ranchi, 1989, pp. 187–198.
35. Wadia, N. H., Desai, H. and Bhatt, M., *Brain*, 1988, **111**, 597 614.
36. Rao, P. V. and Sailapathy, A., *Indian Pract.*, 1965, **18**, 439-442.
37. Roy, S., Gupta, P. C. and Sethi, U., *Neurol. India*, 1972, **20**, 226–230.
38. Gupta, P. C., Roy, S. and Balaya, S., *Indian J. Med. Res.*, 1975, **63**, 101–120.
39. Somasundaram, O. and Menon, M. S., *Indian J. Psychiatry*, 1975, **17**, 108–117.
40. Singhal, B. S. and Dastur, D. K., *Neuroepidemiology*, 1983, **2**, 93-100.
41. Srinivas, H. V., Shankar, S. K., Mehta, B. C. and Saifee, A., *Neurol. India*, 1984, **32**, 33-40.
42. Shankar, S. K. and Satishchandra, P., *Neurol India*, 1988, **36**, 279 283.
43. Dastur, D. K., Manghani, D. K. and Singhal, B. S., *J. Neurol. Sci.*, 1992, **108**, 154 167.
44. Satishchandra, P. and Shankar, S. K., *Neuroepidemiology*, 1991, **10**, 27 32.
45. Ongoing studies and future research plans, *ICMR Bull. HIV Infection*, 1988, **18**, 109 124.
46. Tele, R. D., Parekh, S. J. and Wadia, N. H., *J. Assoc. Physicians India*, 1986, **34**, 549 553.
47. Srinivas, H. V., *Neurol. India*, 1990, **38**, 294.
48. Wadia, N. H. and Swami, R. K., *Neurol. India*, 1970, **18**, 203 218
49. Jeejeebhoy, K. N., Wadia, N. H. and Desai, H. G., *J. Neurol. Neurosurg. Psychiatry*, 1967, **30**, 7 12
50. Dastur, D. K., Santhadevi, N., Quadros, E. V., Gagrat, B. M.,

Wadia, N. H., Desai, M. M., Singhal, B. S. and Bharucha, E. P., *Am J. Clin Nutr*, 1975, **28**, 1255–1270.
51. Satoskar, R. S., Kulkarni, B. S. and Rege, D. V., *Indian J. Med. Res.*, 1961, **49**, 887–896.
52. Mehta, B. M., Rege, D. V. and Satoskar, R. S., *Am. J. Clin. Nutr.*, 1964, **15**, 77–84.
53. Dastur, D. K., Quadros, E. V., Wadia, N. H., Desai, M. M. and Bharucha, E. P., *Br. Med. J.*, 1972, **3**, 260–263.
54. Gopalan, C., *Lancet*, 1969, **1**, 197–199.
55. Shah, D. R. and Singh, S. V., *J. Assoc. Physicians India*, 1967, **15**, 1–8.
56. Shah, D. R., Pandey, S. K. and Rathi, R., *J. Assoc. Physicians India*, 1972, **20**, 575–578.
57. Veera Raghava Reddy, M., *Neurol. India*, 1985, **33**, 161–179.
58. Wadia, N. H., in *Progress in Clinical Medicine* (ed. Ahuja, M. M. S.), Arnold Heinemann, New Delhi, 1979, pp. 489–511.
59. Wadia, N. H., *Neurosciences in India. Retrospect and Prospect* (ed. Pandya, S. K.), The Neurological Society of India, Trivandrum and Council of Scientific and Industrial Research, New Delhi, 1989, pp. 437–507.
60. Niyogi, T. P., *Indian J. Ind. Med.*, 1958, **3**, 3–7.
61. Berry, J. N. and Bidwai, P. S., *Neurol. India*, 1959, **7**, 34–41.
62. Report of manganese poisoning enquiry committee, Ministry of Labour Employment, Govt. of India, 1960, pp. 1–143.
63. Wadia, N. H., *Neurol. India*, 1964, **12**, 29–41.
64. Argikar, A. M., Shah, N. K. and Singhal, B. S., *J. J. J. Group Hosp. Grant Med. Coll.*, 1977, **22**, 1–10.
65. Chuttani, P. N., *J. Assoc. Physicians India*, 1955, **3**, 40–45.
66. Chuttani, P. N., *J. Indian Med. Assoc.*, 1957, **29**, 156–157.
67. Singh, A., Singh, S. and Jolly, S. S., *Neurol. India*, 1959, **7**, 7–8.
68. Bharucha, E. P., Mondkar, V. P. and Varaiya, P. G., Paper read at the 22nd Annual Conference of the Neurological Society of India, Lucknow, 1972.
69. Nagaraja, D., Mukundan, C. R. and Shylaja, *Neurol. India*, 1989, **37**, 315–319.
70. Jayakumar, P. N., Suresh, T. G. and Arya, B. Y. T., *Neurol. India*, 1990, **38**, 259–265.
71. Dhamija, R. M., Madan, V. S., Sanchetee, P. C., Sethi, P. K., Gill, H. S., Sabharwal, R. K. and Saraj Prakash, *Neurol. India*, 1988, **36**, 271–277.
72. Shankar, S. K., Satishchandra, P., Rao, S. L., Vasanth Anisya, Harsha, S., Vani, K. R., Vasudev Rao, T. and Sarala Das, Abstract, 40th Annual Conference of the Neurological Society of India, 1991, p. 10.
73. Jayakumar, P. N., Taly, A. B., Shanmugam, V., Nagaraja, D. and Arya, B. Y. T., *Acta Neurol. Scand*, 1989, **79**, 292–295.
74. Satyanarayana Swamy, H., Anisya, V., Shankar, S. K. and Shashikumar, K., *Neurol. India*, 1991, **39**, 85–88.

ACKNOWLEDGEMENTS. I thank Dr (Mrs.) P. N. Wadia, Dr S. B Desai and Dr S. M. Katrak for giving me some of the prints to illustrate the figures. Miss. V. B Lacca's help with the manuscript is thankfully appreciated.

Pathobiology of Alzheimer's disease: A morphologist's view

S. K. Shankar

Department of Neuropathology, National Institute of Mental Health and Neurosciences, Bangalore 560 029, India

Perhaps no other disease of the human brain has aroused more interest than Alzheimer's disease. The subject continues to be a fertile field for modern neurobiology. The classical morphologic hallmarks include: regional neuronal loss, neurofibrillary tangles (NFT) in neurons and senile plaques (SP) (neuritic plaques) in the neuropil, particularly in limbic and associated cortices. Similar and qualitatively indistinguishable changes occur, though in much smaller numbers, during normal ageing. However, only limited correlation of these lesions with cognitive dysfunction has been reported. NFT consist of highly insoluble paired helical filaments, considered characteristic of Alzheimer's disease, and antigenically related straight filaments. These also accumulate within neurites in and around SP. They are derived from cytoskeletal proteins, particularly microtubule associated protein, tau. In contrast, extracellular amyloid filaments, found in the centre of many of the plaques and in meningeal and cortical vessels, appear to be composed of a hydrophobic, low-molecular weight polypeptide, the β-amyloid protein. It has a novel amino-acid sequence, including a domain thought to be in close association with the plasma cell membrane. Like other amyloids, it is derived from a larger precursor protein and self assembles to form large aggregates. Segments of the β-amyloid protein, when studied *in vitro*, have been found to be neurotoxic to mature neurons and neurotrophic to immature ones. Exactly how these aberrant polypeptides in and around the neurons lead to dementia is still a matter of intense investigation. Recent studies have emphasized synaptic loss as a major correlate of cognitive decline. It will, therefore, be important to investigate the role of β-amyloid in that process.

To explain the evolution and progression of the lesions, a causative role for environmental trace metals has been invoked, but such a role remains unproven. Since it is alleged by some that Alzheimer's disease is not prevalent in India, cross-cultural epidemiologic studies would be of importance. Its age-specific prevalence and incidence in India, however, remains unknown.

ALZHEIMER'S disease (AD) is one of the commonest causes of dementia, a symptom complex characterized by acquired global impairment of intellect, memory and