ensure that the results of a wrong diagnosis are not too catastrophic for the family. This will be difficult because there is much that we do not know about the results of interventional treatment and the danger of leaving an abused child with the family. Sometimes the danger will be great; but at other times the risk may be small and the child will not have to be speedily removed from the parents. We need to be more proficient at determining the degree of abuse and to know more about the long term effects of different sorts of abuse. Just as physical abuse ranges from a single clout by an exasperated parent to recurrent beatings and persistent starving so sexual abuse ranges from an isolated incident of fondling to years of buggery. The danger must vary greatly according to the severity of the abuse and must be weighed against the life that faces the child if he or she is taken away from the parents.

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Neurological clues from environmental neurotoxins

Two reports published last week have given us more information on how environmental neurotoxins may have caused the motor neuron disease, parkinsonism, and dementia seen commonly in Chamorro Indians from the Pacific Islands of Guam and Rota. This new information joins other examples gathered from exotic locations in Asia and Africa in which environmental neurotoxins may have caused human disease. The findings are a rich source of research ideas that may help unravel the cause of these often intractable conditions in developed countries.

The chickling pea, *Lathyrus sativa*, is particularly resistant to drought and in parts of both Africa and Asia its seeds may be eaten in large quantities, especially in times of famine. Consumption of the seeds has long been linked to lathyrisis, a disorder of the corticospinal tract characterised by weakness, spasticity, and muscle cramps that predominantly affects the legs. The disease is endemic in Mysore and the provinces of central India and occurs sporadically in other areas. Last year β-N-oxalylamino-L-alanine, a known constituent of the chickling pea seed, was identified as the likely neurotoxin. When cynomolgus monkeys were fed diets supplemented either with the chickling pea or with pure β-N-oxalylamino-L-alanine they developed tremor, myoclonic jerking, increased tone in leg muscles, and extensor posturing of the hind legs—a syndrome characteristic of monkeys that have recovered from lesions of the pyramidal tract produced at operation.

β-N-oxalylamino-L-alanine belongs to a group of non-protein amino acids that occur naturally in plants and fungi, and several members of the group are neurotoxic in experimental animals. They mimic excitatory neurotransmitters and kill cells by excessively exciting neurones; sustained firing leads to enhanced calcium entry and cell damage. The neurotoxic effect works through specific membrane receptors and is therefore selective for particular types of neurone.

Last week's reports describe a similar series of experiments in which monkeys were fed a related amino acid, β-N-methylamino-L-alanine, and developed a syndrome closely resembling the amyotrophic lateral sclerosis and parkinsonism and dementia complex that previously occurred commonly in the Chamorros of Guam and Rota. β-N-methylamino-L-alanine is present in the seeds of the false sago palm, *Cycas circinalis*, which was a traditional source of food for the Chamorros. Since the second world war the incidence of these diseases on the islands has rapidly decreased, and the decline parallels a decreased consumption of cycad seeds caused by the Chamorros partially adopting an American diet and lifestyle. An interesting observation made during these experiments was that monkeys fed higher doses of β-N-methylamino-L-alanine developed dysfunction of upper and lower motor neurones typical of human amyotrophic lateral sclerosis, whereas those fed lower doses for longer periods developed behavioural changes and extrapyramidal features more like those of human parkinsonism and dementia. This pattern fits that found in humans; amyotrophic lateral sclerosis tends to occur in Chamorros at a younger age than parkinsonism and dementia.

There are other examples of neurotoxins that damage a relatively specific group of neurones within the human central nervous system. One is provided by the cases of parkinsonism that occurred in drug abusers who injected synthetic opiates contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. This substance is selectively active against dopaminergic neurones in the substantia nigra. The specificity of the lesion results from the dopamine reuptake mechanism of these cells that allows them to concentrate toxic amounts of the 1-methyl-4-phenylpyridium ion, a metabolite of methylphenyltetrahydropyridine. The epidemic of spastic paraparesis, known locally as mantakassa, that occurred in a remote northern area of Mozambique in 1981 supplies a third example. This was shown in work carried out in extremely difficult conditions to be caused by dietary intake of cyanogenic glycosides derived from inadequate preparation of the local staple cassava.

The existence of environmental toxins that damage particular populations of neurones raises the possibility that neurotoxins cause some of the degenerative diseases of the nervous system seen in the developed world. This conjecture is strengthened by introducing the idea that exposure to the toxin may have occurred years before the disease becomes apparent. Calne and Langston suggested that Parkinson's disease was caused by environmentally induced damage to the substantia nigra but that the disease might remain subclinical for many years until the inevitable cell loss associated with aging showed the deficiency. A crucial piece of evidence was that damage to the nigrostriatal pathway could be shown by positron emission tomography, even in patients exposed to doses of methylphenyltetrahydropyridine too low to cause symptoms of parkinsonism.

The hypothesis was later extended to include other conditions: the delayed and progressive deterioration that may occur in patients with lathyrisis and poliomyelitis who have been stable for many years, and the latent period between the last head injury and the onset of symptoms of dementia pugilistica. Other evidence that neurological disease may occur after a long latent period comes from a systematic review of prisoners of war from the Far East released in 1945. Eighty nine of these men developed disease of the central nervous system some years after their liberation. Calculation of the numbers of cases likely to occur...
Unconventional viruses and the central nervous system

For several diseases a causative agent has still to be identified. Among these agents are those causing progressive degeneration of the central nervous system such as Creutzfeld-Jakob disease and kuru in man and scrapie in sheep and goats. These are referred to as unconventional viruses but there is no certainty about their composition or physical organisation. Indeed, are they viruses? This question was the focus for much of the discussion at a recent symposium held at the Ciba Foundation.*

Slow virus disease has generated considerable interest not only because of the enigmatic nature of the agents but also because of the similar lesions seen in Alzheimer’s disease and the increasing suspicion that this disease too may be caused by a similar type of agent (though Alzheimer’s disease has not yet been transmitted to animals). Besides being linked by their similar pathological lesions Creutzfeld-Jakob disease, kuru, and scrapie all have a prolonged incubation period, sometimes lasting several years. The first two can be transmitted to apes and monkeys and scrapie can be transmitted to hamsters and mice but even in animals the incubation period is prolonged, making assay extremely slow and inaccurate. This in turn has made identification of the agents much more difficult than usual.

Nevertheless, the presence of about one billion infectious units per gram of brain from a mouse infected with scrapie would appear to someone outside the subject to provide ample material for purification studies. Why, then, has progress been so slow? Apart from the time required to assay the agent the other main reason is the starting material itself. Brain tissue is particularly difficult material to work with and the research worker can never be sure whether the effect of a particular reagent is being influenced by the host material. False suppositions in the early days led to many false starts, with the result that in the past 30 years there have been numerous hypotheses on the nature of the scrapie agent. Recently, however, attention has been focused on three of them.

The first hypothesis is that the scrapie agent is a virus after all, being identical with the scrapie associated fibrils seen on electron microscopy in preparations from infected animals. The virus hypothesis is supported by studies on the kinetics of inactivation of infectivity with different chemical and physical agents. The proponents of this view conclude that the agent contains a nucleic acid with a molecular weight of about one million. Although this is small it is not exceptionally so. Moreover, there are well defined strains of scrapie causing different signs and having different incubation times, which is a clear indication that the agent has its own independently replicating genome. Nevertheless, no scrapie specific nucleic acid has been identified.

The second hypothesis postulates the existence of a virino—a molecular weight nucleic acid together with a protein derived from the host. In this model the nucleic acid is scrapie specific but does not encode any protein, and the nucleic acid of the agent would induce disease by disrupting the regulatory functions of the nucleic acids of the host. Moreover, given that the protein is derived from the host, the absence of an immunological response in infected animals would be explained.

The third and most provocative hypothesis is that the agent is a self replicating protein. The name prion (proteinaceous infectious particle) has been coined by the proponents of this view, who based it on the observation that, although the infectivity of brain homogenates was resistant to various treatments which should destroy nucleic acid, it was destroyed by several protein specific reagents. Moreover, workers have failed to detect any scrapie specific nucleic acid in highly purified infectious preparations of the agent. The major component of these preparations is a protein with a molecular weight of about 30 000, but the gene coding for this protein also turns out to be present in normal brain as well as other normal tissues. Thus apparently the prion protein is encoded in the host genome before infection. The most decisive information about the role of the prion would come from expression of the gene coding for it. If the protein alone is infectious then the product obtained by expressing the gene should also be infectious. So far this has not been shown.

One suggestion is that the prion protein is a component of...