Annotations

Seizures and steroids

For over 40 years we have known that some children with otherwise intractable fits improve with steroids,1 and for over 30 years that a similar response may be obtained with adrenocorticotrophic hormone.2 Since that time a considerable amount of work has centred on infantile spasms, particularly on the relative efficacies of prednisone and adrenocorticotrophic hormone. For each report asserting the superiority of one, it is possible to find another giving the opposite view. Close comparison is confounded by the fact that drugs, dosage, and duration of treatment have varied between the trials. One recent paper3 was unable to find any convincing difference of effect between the two. Despite this, certain facts have emerged; more patients respond to adrenocorticotrophic hormone than to prednisone;4 there are a few, however, who will respond to the latter but not the former.5 The relation between the spasms and hypsarrhythmia is not a close one as the electroencephalographic changes may appear considerably later than the onset of spasms. Recurrence of spasms after hormone treatment is rarely attended by reappearance of hypsarrhythmia and neither the spasms nor the hypsarrhythmia by themselves are likely to affect long term development. What conclusions can be drawn from all this work?

The first and most obvious conclusion is that adrenocorticotrophic hormone acts independently of its effect on the adrenal glands. It is just conceivable that adrenocorticotrophic hormone acts via steroid metabolites intermediate on the biosynthetic pathway; it is difficult otherwise to see how some patients do better on adrenocorticotrophic hormone and a few on prednisone. This also makes the clinical observation that pharmacological doses of adrenocorticotrophic hormone (80 IU) may be more effective than lower doses (20 IU), more plausible. Perhaps, most convincingly, adrenocorticotrophic hormone can control fits in adrenal suppressed patients, including those concurrently on prednisone, even in the presence of documented low serum cortisol concentrations. The most simple alternative is that adrenocorticotrophic hormone has a direct effect on neurons or glial cells, or both.

A second conclusion must be that infantile spasms are associated with almost every condition affecting infants known to the paediatric neurologists. It is unlikely that conditions as disparate as phenylketo-
mus which project to the limbic system, thalamus, and brain stem. It is probable, therefore, that it acts as a neurotransmitter in its own right in specific subcortical circuits. It would be of considerable interest to know if there are functional connections between these cells and those of the pontomedullary raphe complex, which contains a high concentration of serotonergic neurons and which, it has been suggested, may modulate infantile spasms.

One only has to consider the gap between these speculations and our lack of understanding of the mechanism for ensuing mental handicap to see how many unanswered questions remain.

Another steroid responsive movement disorder in children is that of the opsoclonus myoclonus or ‘dancing eyes’ syndrome. This is frequently but not invariably a paraneoplastic effect associated with neuroblastoma. Whether the relation between the neuroblastoma and the brain rests upon a cross immunological basis, on an undescibed neurotransmitter secreted by the tumour, or some other mechanism is unknown, but once again this is a condition that responds dramatically to steroids.

Despite the increasing development of more effective anticonvulsants, it is worth remembering that older children with other types of seizure disorder may also respond to adrenocorticotropic hormone in particular, or sometimes to steroids. Adrenocorticotropic hormone may often be effective in children with somewhat delayed development who display a wide repertoire of seizure types—myoclonus, akinetic, absence, complex, and major motor. It is in these children who have failed to respond adequately to a variety of anticonvulsant ‘cocktails’ that either adrenocorticotropic hormone or a ketogenic diet should be considered. While each has its disadvantages, it should be borne in mind that apart from growth retardation, a Cushionoid face, and general obesity caused by the former treatment, more troublesome side effects such as hypertension and diabetes are most uncommon. It is sensible to keep an eye on electrolyte concentrations as severe hypokalaemia occasionally occurs. It is also good to know that children who are neurologically normal at the onset of seizures and who respond to adrenocorticotropic hormone rarely relapse after a three month course.

It is, however, all too frequent that children who are already neurologically impaired and develop infantile spasms relapse on withdrawal of steroids. Since one is essentially buying time with a course of steroids in these patients, it may be argued that a more rational approach in the first instance is to attempt to control seizures with benzodiazepines or sodium valproate. The recommended dose of adrenocorticotropic hormone varies between 20 and 120 U/day. I usually start with a dose of 40 U/day and then increase it to 80 U/day if after three to four weeks there has been no response. I then wait a further four weeks on this higher dose before concluding that this treatment is ineffective. If it is effective, I continue it for three to six months. If a child is normal initially and responds rapidly to adrenocorticotropic hormone, I would opt for the shorter time. Prednisone is usually started at a dosage of 2 mg/kg/day, and in the event of response, this is reduced to a 10 to 20 mg daily maintenance dose. Switching to alternate day steroids does not seem to result in loss of control. It must be realised that as none of these suggestions have been subjected to controlled clinical trials, they arise from rank empiricism.

Finally, however, one empirical claim deserves consideration. For some time there has been an anecdotal impression in the published reports that early, urgent adrenocorticotropic hormone treatment of cryptogenic patients may preserve them from dementia. The key to this approach lies in the early recognition of infantile spasms for what they are. It is not always realised that before classic ‘salam’ attacks develop, the fits may merely consist of a slight loss of postural tone, producing a momentary dropping of the trunk and dropping forward of the head. Seemingly innocuous, they rarely draw an urgent response from the parents, nor always from the general practitioner. Paediatricians have an important educational role in this situation.

References