We have concluded that the extensive abnormality of CBF demonstrated by PET is indicative of a fixed structural lesion for two reasons. First, the PET lesion was irreversible in the one patient studied a second time (at 90 days). Second, neuropathological correlation demonstrated extensive infarction in the affected hemisphere in the six infants studied post-mortem. We believe the structural lesion to be ischemic in basic nature, primarily because the topography of the lesion, as defined by PET, resides in periventricular vascular border zone regions. Future work will attempt to identify the timing of the ischemia and its precise cause(s) to make possible the ultimate goal, i.e., prevention of the extensive intracerebral involvement.

HIE IN THE TERM ASPHYXIATED INFANT

Hie in the term newborn is the most frequent, recognized cause of the subsequent nonprogressive motor deficits often grouped under the rubric "cerebral palsy". The magnitude of the problem of HIE relates to the essential gravity of the disorder and to its relatively high and unchanging prevalence. Thus, concerning the gravity, approximately 10-20% of infants die in the neonatal period and approximately one-half of the survivors exhibit neurologic deficits. Concerning the prevalence, as many as 1.5/1000 live births exhibit subsequent neurologic deficit secondary to perinatal asphyxia with HIE. To obtain insight into the basic nature and probable pathogenesis of the encephalopathy, we have measured regional CBF in 25 term infants with the disorder.

The clinical features of the infants have been similar. Thus, all have exhibited markedly depressed Apgar scores, presumably secondary to intrauterine asphyxia, which, in fact, was documented in those patients monitored during labor. All infants exhibited the neonatal neurological syndrome that we have described previously as characteristic of HIE in the term infant.

Regional CBF was determined by PET after intravenous injection of $H_2^{15}O$. The major findings were as follows. In the two least affected infants, a distinct outer ribbon of relatively higher CBF was discernible and presumably reflected flow to cerebral cortex. These cortical flows were 50-100% higher than those in cerebral white matter (CBF comparable to that in cortex was also apparent in deep nuclear structures, i.e., thalamus and basal ganglia). In contrast to this apparently normal or near normal pattern of regional CBF, in the remaining patients the pattern of regional CBF was different and quite consistent. The uniform abnormality was a diminution in CBF to parasagittal regions of cerebrum, bilateral and generally symmetric, more marked in posterior than in anterior cerebrum.

We have concluded that at least the major portion of the parasagittal impairment in CBF in these infant represents a fixed structural lesion for three major reasons. First, the PET lesion was irreversible in the one patient who had a second scan (at 20 days). Second, technetium brain scans in five infants showed increased uptake of the radionuclide in the parasagittal regions, bilateral and more marked posteriorly, correlating closely with the PET abnormality. Third, in the one infant who had a postmortem examination, neuropathologic study confirmed softening of cerebral cortex and subcortical white matter in the parasagittal regions, posteriorly more than anteriorly. We believe the structural lesion to be ischemic in basic nature, primarily because of the topography of the lesions, as defined clearly by PET. The particular

vulnerability of parasagittal vascular border zones to systemic hypotension has been shown in experimental models and in adult patients.

CONCLUSIONS

PET scanning provides the capability for determining in vivo critical information about the metabolism and perfusion of small regions of brain. No other technique, currently available or on the horizon, can provide the rapid, serial regional information attainable with this technique. Enormous insight has been gained with PET in adult patients with cerebrovascular disease, epilepsy, dementia, brain tumors and disorders of neurotransmitters and neuroreceptors. Similar insight should be attainable by study of the pediatric counterparts of these adult disorders. Initial studies of the most complex pediatric patients, i.e. critically ill newborns, indicate the feasibility and great value of PET in the study of pediatric disease. We appear to be on the edge of a new frontier in the study of pediatric disease.

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REGENERATION OF THE NERVOUS SYSTEM

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A question of key importance for neurobiology, cell biology and developmental biology as well as clinical medicine, concerns the ability of the nervous system to repair itself after injury. Unlike the peripheral nervous system where considerable regeneration and repair are possible and where function can be restored, the central nervous system is less successful in repairing itself. Recent experiments have shown that given the right conditions neurons within the brain can sprout over considerable distances. One example is provided by the work of Aguayo and his colleagues (1). The principle of these experiments was to make use of the fact that peripheral axons grow extensively along Schwann cells but do not do so along glial cells. A length of sciatic nerve was removed from a mouse and transplanted at one end into a region of the CNS. The other end of the graft was inserted into a distant part of the CNS. Neurons of the CNS were thus given the opportunity to grow along Schwann cells. Retrograde staining of axons with horseradish peroxidase in well-established grafts have shown that intrinsic neurons of different regions of the CNS, such as cortex, thalamus, retina, spinal cord can project over long distances to enter other regions of the nervous system. What is not yet clear is the extent to which synaptic connections can be established by the growing axons at their destination. In other experiments Björklund and his colleagues (2) have shown that embryonic nerve cells known to contain

transmitters such as dopamine can be implanted into adult mouse brains. The embryonic cells not only survive but continue to make their transmitter and release it in the new environment. The embryonic cells can secrete transmitter and correct behavioral deficits in the adult mouse. These and other experiments made on the mammalian nervous system raise the possibility that the prospects for repair might not be as hopeless as had previously been thought. The experiments performed in our laboratory are designed to study mechanisms at the cellular level that enable nerve cells to grow, to grow in a particular direction, to stop growing when they reach the correct destination and there reform synaptic connections with the correct cells but not the incorrect cells (3). The animal used is a simple invertebrate, the leech. Upon such neurons of this animal one can make all sorts of manipulations that would be impracticable in mammalian nerve cells. The central nervous system of this animal can repair itself with amazing fidelity, the correct cells being reconnected to their correct target cells after an injury. At the cellular level it has been possible to show that the nature of the substrate on which the cells are plated has a dramatic influence on their rate of outgrowth. Once targets are reached in culture the connections that are made are highly specific. Some pairs of cells make electrical synapses, other pairs make chemical synapses, other pairs make mixed chemical and electrical synapses and other pairs fail to become connected. With this simplified system it becomes possible to investigate molecular events involved in neurite extension and in synapse formation between specific cells.

It seems inconceivable that highly complex structures such as the visual cortex or the frontal lobes could rewire themselves after injury. Nevertheless, it now seems possible that with better knowledge of cellular mechanisms, progress may be made towards understanding how neurons in the brain can reform their connections after injury.

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PATHOPHYSIOLOGY OF CEREBRAL BLOOD FLOW

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We have previously shown in experiments on fetal lamb that autoregulation of cerebral blood flow is extremely vulnerable in utero. Even if autoregulation is more stable in the newborn lamb (apparently due to higher SaO_2), it is still vulnerable to hypoxia, and is abolished for several hours when SaO_2 drops below 50 per cent. Similarly, 19 stressed newborn infants were shown to have a proportional relationship between flow (intraarterial Xe¹³³ technique) and arterial blood pressure, indicating absence of autoregulation. This entails a risk of ischemia in even moderate hypotension and, conversely, an increased risk of capillary rupture and germinal layer hemorrhage in

hypertension. Of the 19 infants, 8 had neonatal cerebral blood flow $< 20 \text{ ml}/100\text{g}/\text{min}$. Of these three died in the neonatal period. The remaining five were examined repeatedly and were all found to have focal neurologic/neuropsychologic deficits, in contrast to the group with higher neonatal flows who was largely normal.

At 8 years of age single photon emission tomography showed cerebral hypoactivity in watershed areas, in particular in the periventricular region, indicating early ischemic brain damage.

QUANTIFICATION OF ARM-TRACKING PERFORMANCE IN NORMAL AND CLUMSY CHILDREN

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We have investigated whether the performance of normal and clumsy children in a tracking task, could be distinguished quantitatively. The term clumsiness refers to a less than normal competence in fine and gross motor control without evidence of neurological disease. Subjects had to track a target moving unpredictably along a straight line with the left or right arm in conditions of variable difficulty (e.g. with and without a preload, with more or less high frequencies in target movement, with and without visual feedback of arm position). Accuracy of tracking performance is expressed by means of mathematical techniques derived from system theory. The mean delay in the tracking task was significantly larger for clumsy (mean=457 ms, SD=65 ms) than for normal children (mean=395 ms, SD=43 ms). Moreover, the clumsy children tended to be less able to track high frequency target movements (mean cut-off frequency at 1.26 Hz (SD=0.26 Hz) and 1.62 Hz (SD=0.50 Hz) for clumsy and normal children, respectively). Also the coherency between target and tracking signal clearly adds to the possibility of discriminating both groups, suggesting more superfluous movements in case of clumsiness. These differences disappeared or became less clear if difficulty of the tracking task was increased. These results appeared to be reproducible. Still, the performance of a part of the clumsy children was indistinguishable from that of normal children.

PROBABILITY OF NEURODEVELOPMENTAL DISORDERS CALCULATED FROM BRAIN ULTRASOUND APPEARANCE IN VERY PRETERM INFANTS

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To determine the ability of ultrasound scanning of the brain to predict early outcome, the neurodevelopmental status of 342 infants born at less than 33w gestation whose brains had been prospectively scanned was assessed at a median corrected age of 52 weeks (range 44-100 weeks). The probabilities and 95% confidence intervals for neurodevelopmental disorders were calculated according to the ultrasound findings. The results showed that the probability of a major or minor disorder was only 10% (6-15%) in infants whose scans did not show periventricular haemorrhage or markedly increased parenchymal echodensities indicating haemorrhagic lesions in the first week