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 mechnaisms 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 Xe^{133} 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 ml/100g/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

of life, and 11% (8-17%) in those whose scans at discharge gave no evidence of ventricular dilatation, hydrocephalus or cerebral atrophy (loss of brain tissue from any cause). By contrast, the probability of a disorder was 100% (66-100%) in infants with markedly increased parenchymal echodensities in the first week, and 88% (70-96%) in infants with evidence of cerebral atrophy at discharge. 301 of the 342 infants studied could be assigned, on the basis of the ultrasound scan at discharge, either to a large group, comprising 80% of the population, who were at low risk of neurodevelopmental disorders; or to a small group, comprising 8%, who were at high risk: the remaining infants (who had ventricular dilatation) were at intermediate risk of neuro-developmental disorders.

INFLAMMATORY CELLS AND MEDIATORS IN ASTHMA

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Human bronchial asthma is characterised by a widespread and variable intrathoracic airflow obstruction caused, at least in part, by the release of chemical mediators from mast cells and other inflammatory cells. Manifestation of the asthmatic response can be divided into three stages: a rapid spasmogenic phase, a late sustained phase and a subacute, chronic inflammatory phase (1). The immediate response to inhaled allergen has conventionally been associated with the activation of pulmonary mast cells and the release of histamine and spasmogenic products of arachidonic acid metabolism (1). Recent evidence indicates that the IgE-dependent activation of alveolar macrophages (2) and platelets (3) may also be involved. Release of chemotactic factors then leads to a secondary recruitment of further inflammatory cells including neutrophils, eosinophils and monocytes (1). Activation of all three cell types may be involved in late phase responses and in the induction of non-specific bronchial hyperreactivity. Platelet activating factor (PAF-acether) may be essentially implicated in the latter phenomenon (4). The recruitment of eosinophils appears to be critical for the development of many of the clinical features of continuing asthma, including mucus production and desquamation of the surface respiratory epithelium.

While no single cell type can be responsible for all of the manifestations of human bronchial asthma, activation of pulmonary mast cells has been centrally incriminated in the early pathology of the disease. Mast cells are widely distributed throughout the human respiratory tract but those cells lying immediately adjacent to the airways might be expected to be of major importance in modulating the initial phases of the allergic response. These cells would come into immediate contact with inhaled antigens and release their mediators directly onto the airway surface. Such superficially located mast cells may be recovered by bronchoalveolar lavage (BAL) and their properties have been studied in some detail (5-7). In this context, it is important to appreciate that mast cells from different sources, and even from varying locations within a given tissue, may exhibit a marked heterogeneity in their functional properties (8). Current evidence indicates that BAL mast cells in man may represent a particular subpopulation with special characteristics.

Mast cells comprise approximately 0.25% of the total nucleated cells in the lavage fluid of normal individuals and these cells release histamine in dose-dependent fashion on challenge with anti-IgE (5). Most interestingly, increased numbers of eosinophils and mast cells are recovered by lavage of asthmatic subjects and the latter cells show both a high degree of spontaneous instability and an enhanced responsiveness to immunological challenge (7). There is also a significant correlation between the percentage of mast cells in the lavage fluid of asthmatics and measured indices of airflow obstruction (7).

In addition to histamine, anti-IgE induces a dose-dependent release of the newly generated mediators prostaglandin D_2 (PGD_2) and leukotriene C_4 (LTC_4) from both BAL cells and parenchymal cells obtained by enzymic dispersion of whole lung tissue (6). Anti-IgE is more effective in inducing PGD_2 production than histamine release from the BAL cells and maximal ammounts of the prostanoid are generated at lower dilutions of antiserum.

Liberation of PGD_2 is significantly correlated with the percentage of histamine release, suggesting that both mediators are derived from mast cells. The spontaneous generation of LTC_4 is variable and higher concentrations of anti-IgE are required to evoke the de novo production of the eicosanoid. No correlation is observed between the percentage of histamine release and the generation of LTC_4 by BAL cells, suggesting that cells other than mastocytes are involved in its formation. BAL cells spontaneously release more histamine and PGD_2 than dispersed lung cells but the anaphylactic secretion of histamine, PGD_2 an LTC_4 is comparable in the two cases. However, the production of all three mediators is now significantly intercorrelated for the parenchymal cells.

Both BAL and dispersed lung mast cells are thus capable of releasing anaphylactic mediators following immunological challenge. The hyperreactivity and strategic location of the former cells suggests that they may play a major role in human bronchial diseases and provide a useful model for the detailed study of such conditions.

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