sensitivity was obtained, it is difficult to interpret owing to the wide variety of total doses and overall treatment times used and their method of administering oxygen. J. S. Mitchell[24] treated a series of patients with histologically proved carcinoma of the bronchus that had been found inoperable at thoracotomy. Judging the results from those patients who survived more than twelve months after treatment, he found a statistically significant improvement with the use of oxygen at atmospheric pressure. Seven of thirteen patients treated with oxygen survived more than twelve months as compared with only four of thirty-two patients who were treated in air.

The largest clinical trial was initiated by I. Churchill-Davidson and his colleagues in 1954, treating patients breathing oxygen at a pressure of 3–4 atmospheres absolute in a pressure chamber.[25 26] From the first eight patients who were treated evidence obtained from microscopic examination of the irradiated tissues strongly suggested that the addition of oxygen enhanced the radiotherapeutic effect.[27] Subsequently, 108 patients with tumours at many different sites had been treated by the beginning of 1961.[28] The criteria for their selection were: (1) the whole malignant growth, both primary and any secondary deposits, could be included in a radiation field of reasonable size (20 by 20 cm.); and (2) there was considered to be little, if any, chance of cure by conventional radiotherapy. The total number of patients is still small and the time which has elapsed since the treatment of some is short, but in view of the material selected the results are encouraging. Of those who could be assessed 20 (21%) are alive with no evidence of growth for periods up to five years after treatment, and in 41 (42%) there has been apparently complete regression of the primary and secondary growth in the irradiated area. All patients were treated with a much smaller dose fractionation (2–6 fractions) than usual in conventional radiotherapy and over a much shorter period (1–2½ weeks). As would be expected, the smaller and more vascular tumours have shown the greatest "oxygen effect." Particularly interesting features have been the enhanced response of secondary squamous cell carcinoma in lymph glands, which is notoriously resistant to conventional radiotherapy, and the almost complete absence of radiation sickness in spite of the large areas irradiated in some patients and the large doses given in each treatment fraction.

The one serious complication has been an increased incidence of cartilage necrosis. Although in some cases the necrosis has obviously been due to invasion of the cartilage by growth, it is certain that cartilage, which is probably relatively poorly oxygenated, is more liable to damage by *x* rays if the patient is breathing high-pressure oxygen. This was predicted by P. Howard-Flanders and E. A. Wright,[29] who advised making the tumour anoxic and giving three times the normal radiation dose.[30] While it is possible to make a limb anoxic for the period required to give such a dose comparatively few tumours occur in the limbs, and the maximum period for which it is possible to make a whole patient anoxic with safety is under 30 seconds. Even with the most modern and expensive radiotherapy apparatus it is not possible to deliver a dose of the required size in so short a time to deep-seated tumours. It is hoped to avoid the complication by an adjustment of dose level and the use of high-energy irradiation, which is less absorbed in cartilage.

EXPERIMENTAL STUDIES OF CEREBRAL BIRTH INJURY

In recent years more attention has been paid to other than purely traumatic causes of cerebral injury at birth—for example, anoxia. As well as obstetric complications, genetic and biochemical influences can harm the infant, but for the sake of simplicity anoxia and trauma may be considered as the main single agents affecting the brain. Of these two anoxia is the greater danger to the infant at about the time of birth,[1] and it is probably also a common cause of brain injury in newborn babies.[2 3]

The precise mechanism by which anoxia damages nervous tissues is not known, and an elucidation of the biochemical lesions produced may lead to a fresh therapeutic approach to this group of disorders. The brain utilizes glucose almost exclusively for production of energy.[4] Experiments on animals deprived of oxygen have shown that lowering the blood sugar shortens their survival,[5] and in addition that hypoglycaemia alone can produce brain lesions similar to those produced by anoxia.[6] High-energy phosphate compounds are used in the brain to provide energy to maintain the integrity of the cell membrane, and D. B. Tower[7] has shown that in the central nervous system during anoxia the level of creatine phosphate falls and that of organic phosphate rises. However, A. Geiger has presented evidence that such energy can be produced in the absence of carbohydrate substrate,[8] and that electrical activity could be maintained in the absence of glucose if nucleotides were present. In the light of this it is interesting that H. E. Himwich[9] found that nucleotides could protect newly born animals from the effects of anoxia.

A further complication to the biochemical intricacies of brain metabolism is the difference in

response to lack of oxygen of mature and immature animals. J. B. Ranck and W. F. Windle,[10] for example, have produced asphyxial cerebral damage in newborn monkeys which has involved only brain-stem nuclei, sparing the cerebral and cerebellar cortices—which are highly susceptible in the adult. The observation that newborn animals are relatively resistant to anoxia has recently been correlated with their ability to increase rapidly the rate of glycolysis when the oxygen supply is reduced.[11] Survival of the newborn animal in an atmosphere of nitrogen depends on the presence of glycogen in the myocardium,[5 12 13] and when this is depleted the circulation fails. Although in the young animal the heart is more susceptible to lack of oxygen than is the brain,[14] J. C. Mott[12] points out that the brain requires glucose and an efficient circulation, and that these will be lacking if the heart fails. The explanation of such peculiarities of response in the newborn animal is largely speculative. We do not yet understand enough about the maturation of enzyme systems,[15] salt and water metabolism[16 17] in the brain, and the functions of the blood–brain barrier.[18]

In man, epidemiological investigations have shown a positive correlation between intellectual subnormality and cerebral palsy on the one hand and, on the other, obstetric complications,[19] prolonged apnoea at birth,[19] maternal anaesthesia during labour,[20] and other evidence of perinatal anoxia.[21] The association between prematurity and cerebral palsy,[22] when not due to severe jaundice of the newborn, may partly depend on the greater susceptibility of these infants to anoxia,[3] but perhaps we are not yet able to pinpoint a single factor such as this. Necropsy studies[3] have shown that the subarachnoid and intraventricular haemorrhages in the newborn are due to anoxia, while subdural haemorrhages are always traumatic in nature. Chronic brain lesions such as gliosis or cavitation of the centrum semiovale, loss of neurones in the cerebral cortex or basal ganglia, status marmoratus, and ulegyria may also be due to damage at or near birth,[2] but in each individual case it is difficult to assess whether trauma or anoxia is the more important factor or whether other influences are operative. Retrospective epidemiological studies on children with cerebral palsy have indicated that mechanical factors are less important[23] and that the proportion of cases due to trauma is declining as obstetrical practice advances.[24] A question of great clinical importance arising from these studies is whether the magnitude of brain damage is proportional to the degree of anoxia or other stress, or whether a threshold exists the level of which is determined by genetic or environmental factors.

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THE PANCREATITIS PROBLEM

There are two classical theories to explain the aetiology of acute pancreatitis. E. L. Opie's[1] theory of biliary reflux into the pancreatic duct is the one most supported by surgical and post-mortem findings. The case described by Opie which led to the introduction of his theory was an unusual one, for a gallstone had become impacted at the sphincter of Oddi. It is, however, an interesting fact that acute pancreatitis is found almost exclusively in patients with a common termination to the main pancreatic and common bile ducts. Although a gallstone impacted as in Opie's case is unusual, the biliary apparatus commonly is diseased in acute pancreatitis, gallstones being found in the gall-bladder in about 50% of cases.

The second theory, propounded by A. R. Rich and G. L. Duff,[2] is based on the observation that epithelial hyperplasia can be found in the pancreatic ducts in some cases, and it was believed that intrapancreatic obstruction could be produced by this change. This in turn might initiate the chemical changes which lead to the onset of acute pancreatitis. Some observers feel that these histological changes are of little importance in the aetiology of acute pancreatitis, though they may result in fibrosis and atrophy of the gland.

In a recent review D. A. Dreiling[3] discusses some of the other factors which may be significant in the development of acute pancreatitis. Secondary vascular changes may have a role in converting localized inflammatory changes into those of frank tissue necrosis. Spasm of the sphincter of Oddi, though a difficult factor to assess, could be important in the initiation of the acute pancreatitis complicating alcoholism, particularly as alcohol stimulates the gland to secrete. Autoimmune and allergic factors are apt to be invoked as causes of disease when more usual causes are difficult to find, and they have also been put forward as possible causes of acute

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