Section of Neurology

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DISCUSSION ON THE CLINICAL CONSEQUENCES OF CEREBRAL ANOXIA

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The industrial aspects of anoxia have lost much of their former significance owing to improved conditions and ventilation in factories and workshops. Unfortunately the same cannot be said of domestic and accidental coal-gas poisoning which causes some 500 deaths annually in England and Wales (Thelwall Jones, 1955) and is one of the chief sources of anoxic admissions to hospital. Hypoxic effects are seen too with comparative frequency in medical practice, and, as these do not always receive the recognition that is their due, I propose to refer briefly to them first.

HYPOXIC EFFECTS IN MEDICAL PRACTICE

They arise as side effects of injury, disease or as a consequence of medical or surgical treatment. Cerebral circulatory failure, dehydration, the incautious use of barbiturates or other potentially histotoxic drugs, and disturbances in electrolyte balance are the most common exciting causes.

Under normal metabolic conditions the brain is the most susceptible of organs to reduction in its oxygen supply. Not only must oxygen be available, but the cerebral blood flow must be adequate; it is not surprising therefore in medical practice that cerebral circulatory failure should be one of the chief causes of hypoxic effects. Two ways in which these may be brought about are: (1) By failure of the pumping action of the heart, (2) by diminution in the total blood volume, whereby the work of the heart (however efficient it may be) is rendered ineffectual. Typical examples of the first kind are cardiac arrest and chronic congestive heart failure. Patients in chronic congestive failure become irritable, drowsy, confused and disorientated because their cerebral blood flow is slowed and cerebral oxygen consumption significantly reduced (Scheinberg, 1950). Exsanguination from post-partum or gastro-intestinal hæmorrhage is an instance of the second kind.

Dehydration and electrolyte imbalance.—The examples so far given are fairly concrete; anoxic symptoms are so pronounced and the cause so patent that there is little difficulty in their recognition. But for each classical example of anoxia seen in practice there must be five or more other cases in which the mechanism is not so clear, or in which more than one factor causing anoxia is at work. Thus, toxic-confusional reactions are often seen in patients whose fluid intake is inadequate; where there is vomiting or diarrhœa, or where fluid is being lost in some other way, so that, unless it is replaced, dehydration and disturbance in electrolyte balance result. It is not so long ago since the cerebral symptoms of dehydration were attributed to increased permeability of the blood-cerebrospinal fluid barrier permitting toxins from the alimentary tract to reach the brain, but it is now known that dehydration exerts its effects by causing diminution in cerebral blood flow and creating stagnant hypoxic conditions. Mishaps of this kind are liable to occur especially in elderly arterio-sclerotic persons, e.g. after operations for cataract, and illustrative cases have been described elsewhere (Allison, 1952).

Chronic duodenal ulcer is another source of such cases. Here, in addition to dehydration the noxious effect of alkalosis may be added, as was first noted in this country by Cooke (1932). Alkalosis is especially liable to occur in cases where there is renal damage, pyloric obstruction or excessive use of alkalis. Although probably less potent in its effects than dehydration, alkalosis induces cerebral hypoxia by high blood pH levels interfering with dissociation of oxyhæmoglobin. It is not often one has either the opportunity or means of confirming this statement but, through the courtesy of Professor G. M. Bull, I have learned of a case which I have his permission to mention.

Case I.—A man of 39 who had been in the habit of taking alkaline stomach powder five times daily for some years on account of dyspepsia associated with chronic duodenal ulceration. Although there was no radiological evidence of obstruction, he had been vomiting, and on admission to hospital was in a drowsy, confused mental state, resisting examination. The results of investigations of the blood are as follows (normal values in brackets) : Packed cell vol. 32·5% (48%), plasma vol. 1·33 l. (3 l.), total blood vol. 1·97 l. (6 l.), blood urea 622 mg.% (20–40 mg.%), chlorides 450 mg.% (365 mg.%), Na 309 mg.% (330 mg.%) CO_2 comb. power 100 vol.% (55–70 vol.%), blood pH 8·0 (7·25), Effective renal flow 15 ml./min., glomerular filtration rate 5 ml./min., urine flow 2·5 ml./min. Samples of blood were taken from the internal jugular vein and oxygen saturation was found to be 33 and 38% in two samples. Allowing for the pH of the blood at the time, and reading from

Barcroft's curves for oxyhæmoglobin dissociation at different pHs, oxygen saturation in the cerebral tissues must have been about 8–10 mm.Hg in comparison with the normal figure of 35 mm.Hg.

Hypoxic symptoms often mistaken for hysteria.—There is another point relating to the symptoms displayed by these patients. In sick persons the symptoms of hypoxia are less sharply defined than they are in healthy subjects. When a healthy person is exposed to hypoxia his sudden unaccountable muscular asthenia, aggressiveness, absentmindedness or senseless repetition of actions at once draw attention to him. Textbooks stress these points but, in persons already sick and confined to bed, such premonitory symptoms as headache and blurring of vision may pass unnoticed and disturbances of behaviour, due to the clouding of consciousness, may readily be mistaken for hysteria. It is important in such cases always to look for signs of perseveration which is a reliable guide to the presence of organic clouding of consciousness, and usually pathognomonic of it. A simple test is to ask the patient to put out his tongue and then, when he has done so, to close his eyes. Perseveration may also be apparent when a patient, having repeated the days of the week correctly, and being asked to name the months of the year, goes on repeating the days. Another useful guide to the presence of organic clouding of consciousness is inability to reverse simple series, e.g. counting from 1 to 20 and then counting backwards from 20 to 1. A third reliable indicator is the presence of disorientation, loss of temporal and spatial orientation being usually indicative of deeper clouding of consciousness than the presence of temporal disorientation alone.

Clinical Effects of Severe Anoxia

These minor hypoxic effects, which I have emphasized purposely, are usually recoverable and due to reversible changes in cellular function; the same applies to many cases of coal-gas poisoning. In the majority of these full consciousness is regained within a few hours, recovery is uneventful and there are no sequelæ. The plantar reflexes at first are often extensor in type, but they quickly revert to normal, the sign when present alone having no particular significance.

Prognosis as to survival.—When anoxic exposure is severe death usually results without the patient regaining consciousness. It follows that when the duration of anoxia is unknown, and the patient still unconscious when first seen, it is extremely difficult to estimate the prospects of survival. Dilatation of the pupils, the recurrence of repeated epileptiform fits and sweating are ominous features, but otherwise one cannot judge by the clinical signs alone. Thus one patient, a woman aged 60 and the victim of accidental coal-gas poisoning, was unresponsive to painful stimuli, breathing stertorously and displaying conjugate deviation of the eyeballs. Her limbs were rigid, the arms flexed at the elbows and wrists, the legs extended and the plantars doubly extensor. Yet she recovered full consciousness within eight hours, whereas another patient suffering from coal-gas poisoning whose condition was very similar, a young man aged 25, remained in coma and died on the third day. The difference lay not so much in the clinical signs they presented as in the relative severity of their exposures to anoxia.

Survival after severe anoxia is rare and purchased as a rule at the cost of irreversible and widespread damage to the nervous system. My own personal experience of such instances, over a period of several years, amounts only to 15 cases. In all of these cases initial recovery of consciousness was slow, coma or drowsy stupor persisting for twelve to forty-eight hours and full consciousness not being regained for several weeks or months. Survival is improbable when coma persists for twenty-four to forty-eight hours but de Ajuriaguerra and de la Vigne (1946) have reported recovery in several cases after coma had lasted from 48 to 70 hours. As regards the validity of claims for compensation in industrial accidents, Hunter (1955) states that, to be considered reasonable, there should be, not only clear evidence of anoxia, but continuous unconsciousness for at least six hours after return to the fresh air.

Before considering the neurological sequelæ of anoxia there are two other aspects of prognosis which require mention. First, *unexpected recovery after severe anoxia* is extremely rare but authentic instances are on record. For example, Kossmann (1947) reported the case of an airman whose oxygen failed at 25,000 feet for a period of ten minutes, and there is Turner's (1950) case of a young man whose heart stopped beating for seven minutes. Three minutes of cardiac arrest usually results in irreversible damage to the brain (Lucas, 1953), but in this case, although for a year or more the patient showed signs of impaired cerebration, after two years he had recovered and there were no traces of his former disabilities.

Also remarkable was the case of a woman of 70 seen in 1947 who showed no permanent ill-effects after severe coal-gas poisoning (Allison, 1950). Unaware of a leak in the main gas pipe, she and her husband (also aged 70) retired to bed one night and were not discovered until forty-eight hours later, when neighbours broke in and found the couple still in bed, the man dead and the woman in deep coma. For the first two days she lay in semi-coma but by the third day showed signs of recovering consciousness, when it was apparent she

had a right-sided hemiplegia. By the seventh day she was wakeful, able to sit up and the hemiplegia was improving. She could make small talk but was totally disorientated in time and space and confabulating freely. Her mood was one of fatuous euphoria and in this state she remained for eighty-eight days. By then, however, all traces of residual hemiplegia had disappeared and she had regained orientation, memory for past events and insight. There was no sign of subsequent deterioration, and she was seen at frequent intervals throughout the next two years. Unfortunately when she died later of bronchopneumonia, no post-mortem examination was carried out.

Second, *temporary survival* in a comatose or vegetative state is also uncommon. Thus, a case fully reported by Pineas (1924) lingered for seven weeks whereas Howkins, McLaughlin and Daniel's (1946) case died on the twenty-sixth day. Until recently I had not seen such a case survive for longer than a few days. However, I have had one recently where the survival period was nearly six months.

Case II.—A child aged 7, whose heart stopped beating for ten minutes on October 13, 1955, death not occurring until April 2, 1956.

For the first three days after the anoxic experience she remained in deep coma; on the fourth day weak withdrawal responses were elicited to painful stimuli. Recurring tonic convulsive seizures were then seen between the third and tenth day, in which the head became retracted, limbs extended, trunk arched, wrists and fingers strongly flexed and feet plantar-flexed. After these fits had ceased spontaneously, about the tenth day the child was observed to show some change of facial expression when her mother spoke to her insistently, and it was evident she could hear although she was blind. A few days later, before the end of October, respiration was accompanied by phonation and the limbs were beginning to show signs of increasing spasticity. From that time there was no further improvement. About a month after the onset she developed torsion dystonia (Fig. 1) and involuntary trombone tremor-like movements of the tongue (Fig. 2). These recurred frequently whenever she was disturbed and continued at the rate of 2–4 per second for several minutes at a time, chewing movements of the lower jaw occurring simultaneously. However, they ceased spontaneously after three to four weeks and, like the fits, did not subsequently recur.

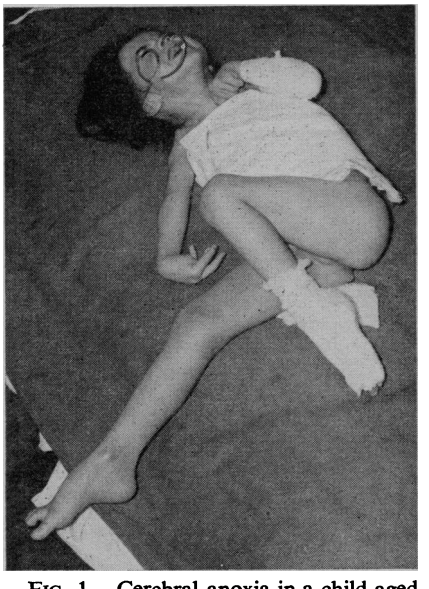

FIG. 1.—Cerebral anoxia in a child aged 7. Photograph taken one month later, illustrating posture of torsion dystonia.

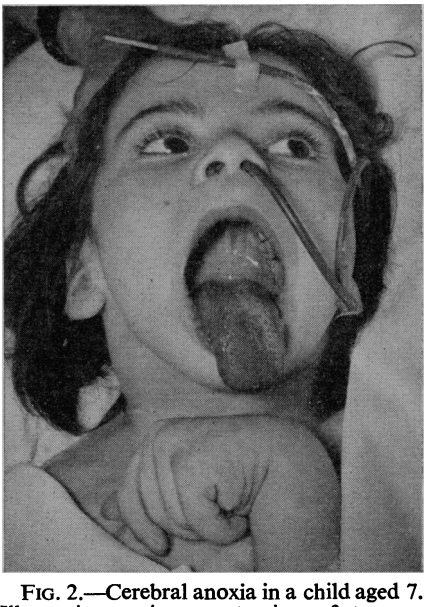

FIG. 2.—Cerebral anoxia in a child aged 7. Illustrating curious protrusion of tongue, which was the site of rhythmical involuntary movements.

Although this little girl was seriously and permanently disabled, incapable of utterance other than crying and phonation, and blind, there was evidence (apart from circumstantial observations at the bedside) that she was capable at times, of some cerebral activity and that her hearing was relatively intact. A completely flat record was obtained on electroencephalography. Haglund (1952) obtained a similar result in an anoxic decerebrate infant. In my patient the featureless character of the record could not be altered by causing her to breathe pure oxygen or mixtures of oxygen and carbon dioxide. Stroboscopic stimulation had also no effect. However, the effect of slowly injecting Pentothal Sodium intravenously

was to set up some slow wave activity at frequencies of 2–3 c/s. That some hearing was retained and that she was capable of attending to certain stimuli was shown when a favourite toy—a musical box—was placed beside her and played; at once her breathing became faster and frequent blinking movements of the eyelids were observed.

Neurological Sequelæ in Survivors After Severe Anoxia

The principal features seen in the 15 cases with neurological sequelæ are as follows:

S. M'C., male, aged 47. 6.8.52. Electrocution. Retrograde amnesia of some minutes, post-anoxic amnesia three days. Chronic amnestric syndrome with expressive dysphasia and reading disability, constructional apraxia.

B. M'C., male, aged 60. 29.5.50. Respiratory arrest at operation; comatose for twelve hours. L. hemiplegia (after some days). Jargon aphasia at first; later persistent nominal defects and agraphia with visual object agnosia and constructional apraxia. Chronic amnestic syndrome.

J. M'D., male, aged 41. 13.6.52. Two minutes' cardiac arrest during surgical operation for mitral stenosis (valvulotomy). Coma followed by incoherent talk, muttering delirium. No dysphasia but grossly disorientated. Cortical blindness. R-L disorientation and finger agnosia. Death after some months.

D. M., male, aged 19. 20.7.55. Cardiac arrest during surgical operation. R. hemiparesis and sensory impairment with half visual field defect; later objects recognized on previously blind side but visual inattention persisted. R-L disorientation, dyscalculia, occasional finger agnosia. Constructional apraxia. Improving.

R. M., male, aged 70. 7.2.50. Accidental coal-gas poisoning. Retrograde amnesia of some hours, post-anoxic amnesia 1 week. Transient finger agnosia and R-L disorientation with constructional apraxia but recovered fully.

A. B., male, aged 56. 19.1.53. Cardiac arrest during surgical operation. Status epilepticus with myoclonic jerking. Decerebrate posture. Death on fourth day.

A. N., male, aged 7. 21.6.53. Respiratory difficulties during an abdominal operation. Status epilepticus. Decerebrate rigidity. Death on tenth day.

F. C., female, aged 22. 26.7.55. Valvulotomy. Cortical blindness, disorientation, perseveration. Partial recovery of vision but persistent defects chiefly in R. half field.

G. C., male, aged 22. 19.6.46. Coal-gas poisoning. Remained in semi-coma. Death on third day.

L. R., female, aged 70. 25.11.47. Accidental coal-gas poisoning. Prolonged post-anoxic psychosis. R. hemiplegia. Constructional apraxia. Ultimate recovery.

L. M., female, aged 6. 13.10.55. Cardiac arrest during abdominal operation. Survived for six months. Status epilepticus, involuntary tongue movements, postural dystonia, blindness.

W. M., male, aged 24. 28.11.43. Anoxic as result of an explosion on board ship. Prolonged post-anoxic psychosis followed recovery from coma. Later signs of Parkinsonism and chronic amnestic syndrome supervened.

M. B., male, aged 47. 16.5.42. Anoxic as result of an explosion on board ship. Prolonged post-anoxic psychosis. Later showed constructional apraxia and developed chronic amnestic syndrome.

F. H., male, aged 31. 16.5.42. Anoxic as result of an explosion on board ship. Post-anoxic psychosis with amnesia of several weeks' duration. Later developed chronic amnestic syndrome with paraphasia and constructional apraxia.

O. B., male, aged 47. 16.5.42. Anoxic as result of an explosion on board ship. Post-anoxic amnesia one week. Developed a chronic amnestic syndrome with constructional apraxia and signs of Parkinsonism.

Epilepsy was seen in 3 patients; in 2 the development of status epilepticus heralding death, and in the third (the case described earlier), a residual state of partial decerebration. In one of these cases of status epilepticus, a man aged 56 (A. B.), not only did fits recur until death, but in the intervals between them there was myoclonic jerking of the limbs, face and jaws. These were most pronounced and occurred spontaneously although they could be elicited by tapping over muscle, by stimulation with a flashing light or a sudden loud noise. They could not be evoked by pin-prick, to which the depth of unconsciousness had apparently rendered the patient insensitive.

Three of the patients developed *hemiplegia* but ultimately recovered full function of their limbs. Hemiplegia, when it occurs as a sequel of anoxia, is usually not apparent for some days, and reaches its maximum between the seventh and fourteenth days. In one case (D. M.), it was accompanied by gross sensory impairment and neglect of the ipsilateral arm, but I have not seen any cases with gross disturbances of body image as have been described by Solomon (1932).

In 2 cases *Parkinsonism* was observed. Like hemiplegia, its development takes place insidiously some weeks or months after anoxia. In one of de Morsier and Georgi's (1940) cases symptoms were apparently not noticeable until a year had elapsed. In my cases the symptoms were mild in their extent: coarse tremor of the tongue of trombone type, plastic increase of tone in the limbs, facial immobility, and in one case there was typical pill-rolling tremor. Both cases were followed up, and in one (W. M.), the signs were no longer apparent two years after the anoxic event. Nielsen (1943) has reported similar recovery after three

years. Incidentally, another anoxic patient, not included in this series, was already suffering from post-encephalitic Parkinsonism when, in a fit of despondency, he attempted to gas himself; although several hours unconscious, he recovered and displayed no evidence of worsening in his neurological status. Yakowley (1944) described old cystic areas of softening distributed symmetrically in the pallidum of a man surviving forty-nine years after gas poisoning. Grinker's (1926) fully detailed case only survived two months.

Passing to the incidence of residual defects in intellectual function, these may be considered first as regards symptoms which could be attributed to general "knocking off" of cerebration, changes in mood and behaviour, impairment of memory for past events and disorientation. All of the survivors showed defects of this kind. As regards more specialized defects, residual disturbances of *speech* after consciousness had been regained, were seen in 4 cases. One patient (B. M'C.), showed a babble of talk amounting to jargon aphasia for some weeks but more often anoxic survivors are silent and bereft of spontaneous speech, or if they speak do so hesitatingly, leaving sentences unfinished. Many of them have difficulty in naming objects and perseveration is partly responsible for this difficulty; they are better at naming sighted objects than doing so from memory and make little use of gesture and periphrasis. In one case (F. H.), there was a marked paraphasia four months after he had been rendered anoxic. He was euphoric, but partly aware of his speech difficulty for he admitted that when he could not remember a name he did his best to improvise. There was impairment of articulation, and this (with his paraphasia) rendered speech almost unintelligible at times. At other times he was fairly good and could name common objects correctly. But when shown a picture of a tent he described it first as "a camp", then as "a hut" ... 'trench"... "tent" A picture of a bear he described as "a tiger" ... "leopard" ... "beast".

Blindness was a sequel in 4 cases. In one of these, L. M., the child with postural dystonia, there was marked papilloedema and retinal congestion. In 3 other cases blindness was of cortical type, although one found it most difficult to be sure about this (B. M'C., J. M'D., F. C.). However, by comparison with the case reports of others (Adler, 1944; Wechsler, 1933) they appeared to fall within this group. Thus in one case (F. C.), a young woman with mitral stenosis, whose symptoms followed an operation for valvulotomy, consciousness was regained on the first day, but on the next she complained of inability to see and became greatly distressed. Those in charge of her case were inclined to think her hysterical as, indeed, seemed likely at the time. Cerebral embolism was considered unlikely as no clot had been found in the auricle at operation, there was no calcification and the heart sounds were regular. However, the pupils were semi-dilated and reacted only sluggishly to light. She could tell when light was flashed in her eyes but was unable to recognize any objects. There was marked perseveration in action and speech and she was totally disorientated in time. Vision recovered within a week sufficiently to enable her to recognize objects, but she is left with permanent field defects chiefly in the left half field.

In the other cases in which repeated observations were made the pupillary responses to light varied from day to day, usually being present and sluggish, but occasionally absent. As in the foregoing case there were no disc changes. The existence of blindness was not recognized by either of them and the symptom was associated with temporal and spatial disorientation, a mood of facile euphoria, difficulty in repeating days of the week backwards, defective registration and recall of fresh data. Anosognosia was pronounced and in one case (J. M'D.), there was, in addition, right-left bodily disorientation, and inability to count or to name the fingers. Despite these defects this patient showed no speech disturbance and had no difficulty in recognizing the nature of objects by touch or in some instances, by hearing. He displayed no ideomotor apraxia.

Performance from day to day in these patients with cortical blindness varies considerably. One day they may recognize some objects and not others, another day fail entirely to recognize anything. Disturbances of figure-background relationships can often be demonstrated by holding up an object and asking the patient to identify it; he may peer intently in the general direction, his hand stretching out exploringly and taking another object, e.g. a handkerchief protruding from the examiner's coat pocket. Similarly, in cases where cortical blindness is transient and recoverable, a stage may be reached when an object is identified without difficulty against a plain background but not against an assortment of other objects. Affective influences also appear to play some part in determining which objects are recognized.

All anoxic patients were tested for signs of *Gerstmann's syndrome* but this was found only on three occasions. Finger agnosia and right-left disorientation are believed to represent disorders of body imagery, but it has been suggested that right-left disorientation may be due to semantic errors on the part of the patient, arising out of associated speech disturbance. However, in all three instances in which the syndrome was present, general spatial and temporal disorientation co-existed, and when this was regained right-left disorientation and finger agnosia disappeared. This suggests that the two are related, right-left disorientation being a fragment of total disorientation and not the result of semantic errors. Further, one

has the impression that during recovery of consciousness patients first became aware of their bodies and later of their environment, and this may account for the comparative infrequency of the syndrome at a time when there is still gross general spatial disorientation.

By contrast, *constructional apraxia* is seen with greater frequency in post-anoxic cases. Ideomotor apraxia is well recognized and several instances of it have been reported in the literature, but it is more a symptom of the earlier stages of recovery of consciousness. Constructional apraxia may persist (almost as an isolated residual defect) for some weeks or months after full consciousness has been regained. This is an important point for, if allowed to return to work, such patients get into immediate difficulties through their inability to undertake any formative or creative tasks, whether these involve the assembly of complicated apparatus or simply laying the table for tea. Sticks or match tests (after Goldstein), Kohs' blocks or drawing tests have been used as simple clinical tests for uncovering the defect and have proved most valuable.

The fact that constructional apraxia is encountered so often in post-anoxic states, and that it tends to disappear in time, leads one to think that, like Gerstmann's syndrome, it cannot be related solely to a focal lesion in one part of the brain, but that it depends for its existence on widespread disturbance of function in both hemispheres. Indeed the clinical consequences of anoxia afford unrivalled opportunity for investigation in this field. The biochemical lesion may affect some parts of the brain more than others, but it probably does so more or less diffusely and symmetrically. Consequently, in recoverable cases (and these form the majority) one can observe the different phases through which cerebral functioning must pass between total dissolution and final reintegration, By doing so it is possible further insight may be gained into the mode of production of such symptoms in patients with purely focal cerebral lesions.

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Transitory mental confusion is almost a normal concomitant of illness in old people (Bedford, 1954). It is usually a non-specific manifestation, of no localizing value, of disease or disturbance often quite remote from the brain. There are four main reasons for the brain in old age being so sensitive an "indicator" of disordered function anywhere in the body:

(1) The brain at any age is extremely vulnerable to anoxia (Courville, 1939; Hoff *et al.*, 1945; Corday *et al.*, 1953) because of its complete dependence on the aerobic production of energy from glucose (Himwich, 1951). The relative immunity to anoxia of the brain of the newborn which might be expected theoretically owing to the short-lived persistence of anaerobic glycolysis as a source of energy (Himwich, 1951) is not clinically apparent (Read, 1955).

(2) The brain is probably more sensitive to lack of oxygen than any other organ or tissue of the body. Not all parts of the brain are equally sensitive, however; consciousness is lost within 45 sec. in complete oxygen-deprivation; the cortical neurones in the supra-granular laminæ cannot survive more than 4 min. of anoxia; and 10 min. is probably the outside limit for survival of any of the nerve elements of the brain (Hoff *et al.*, 1945).

(3) The supply of oxygen to the brain is dependent upon the state of the heart, the lungs, the blood and the blood vessels; the composition of the respiratory gases; and the integrity of such homœostatic mechanisms as the sino-aortic and spinal baroceptor reflexes. Cerebral cellular metabolism derives its energy from oxygen and glucose but also depends upon a supply correct in amount and proportion of ions including Na, K, Ca, H, and phosphorus, and substances including water, amino acids, fats, glucose, enzymes and co-enzymes: these

in turn are dependent upon the state of the liver and kidneys. the endocrine glands (for such substances as insulin and thyroid hormone), the intestines and the composition of the diet.

(4) The cerebral circulation tends to become impaired in old age (Himwich, 1951) and derangement of function of other organs occurs more readily because of their lowered "reserve".

It is, therefore, not surprising that the brain in old age is a sensitive "indicator" of disordered function anywhere in the body, and that geriatric practice provides a fruitful field for a study of the clinical effects of cerebral anoxia. These reasons also explain why the effects of cerebral anoxia are usually non-specific in the sense that the same clinical pattern may be produced by widely different ætiological factors.

It may be useful here to recapitulate briefly some physiological principles relating to cerebral anoxia—by which is meant a condition of oxygen lack in the brain from any cause.

Four types of anoxia are still generally recognized: (1) Anoxic—when the oxygen tension in the blood is lower than normal. (2) Anæmic—when the amount of functioning hæmoglobin is reduced but the arterial oxygen tension is normal. (3) Stagnant—in which the blood supply to the tissues is insufficient but the arterial oxygen tension is normal. (4) Histotoxic—when the cells are unable to utilize effectively the oxygen supplied to them.

(This classification is arbitrary and incomplete. For example it takes no account of the essentially anoxic effect of hypoglycæmia or disturbances in the potassium-sodium-calcium ratio: these, however, can be "forced" into the "histotoxic" group.)

Certain types of anoxia are potentially more dangerous than others, the deciding factor being the availability of oxygen to and within the cells. For example, in anoxic anoxia due to the respired atmosphere being poor in oxygen, the lowered oxygen tension in the blood stimulates breathing and results in CO_2 being "washed out" of the blood. Thus, not only is there too little oxygen in the blood, but the oxygen which is present is less readily available to the tissues because the concomitant reduction in CO_2 tension impedes the dissociation of oxyhæmoglobin—the curve is "shifted to the left". In these circumstances, any increased demand by the cells for oxygen may further aggravate the anoxia.

Again, the anæmic anoxia of carbon monoxide poisoning is much more serious than a hæmorrhagic or Addisonian anæmia in which the amount of functioning hæmoglobin is reduced to the same degree; for carboxy-hæmoglobin impairs the dissociation of oxyhæmoglobin and so the oxygen which *is* present is less readily available to the cells. Similarly the histotoxic anoxia due, for example, to narcotic drugs or cyanide is potentially very serious for the cells are rendered unable to utilize the oxygen supplied to them. There is a parallel between this type of anoxia and the effect on the brain of hypoglycæmia in which the cells are unable to utilize oxygen by being deprived of the energy mechanism for doing so.

There are, as has been indicated above, very many conditions which may produce cerebral anoxia (Bedford, 1955) including cerebral circulatory failure from any cause (Corday *et al.*, 1953) and general and cerebral metabolic disturbances (Allison, 1952). In clinical practice, it is often not possible to determine with accuracy the immediate cause of damage, for multiple factors and more than one type of anoxia frequently coexist in the same patient.

Examples of some factors which should be constantly borne in mind are as follows:

(1) The routine (and therefore indiscriminate) prescription of such drugs as morphine, atropine, hyoscine and barbiturates as pre-operative and post-operative medication to patients young and old, and without knowledge of the individual's sensitivity to them.

(2) Pyrexia and toxic-infective states (e.g. cystopyelonephritis following prostatectomy) render the brain more susceptible to anoxia by increasing its basal oxygen consumption (Himwich, 1951). This may well be a factor in the development of the dementia seen occasionally after prostatectomy (Bedford, 1955).

(3) The sino-aortic and spinal baroceptor reflexes which normally maintain cerebral blood flow may be abrogated in general and spinal anæsthesia and in the hypotension deliberately induced with the methonium and allied compounds to facilitate surgery. Blood supply to the brain may thereby be imperilled and risk of cerebral anoxia enhanced by such otherwise innocuous manœuvres as movement of the patient or alteration in his posture.

I shall not attempt a comprehensive survey of the clinical effects of cerebral anoxia. Some are adequately dealt with in the standard textbooks of physiology, aviation medicine, pædiatrics, anæsthesia, &c.; others, e.g. cough syncope, have recently been intensively reinvestigated; some have been described by Dr. Allison. The effects of sudden, subacute and chronic anoxia in healthy adults are well known—due in great measure to heroic experiments performed on themselves by physiologists and naval and air-force volunteers. (It is perhaps surprising that the Air Forces of this country and the U.S.A. have no record of examples of permanent damage to the brain in survivors of aviation anoxic episodes (Campbell, 1955; Kilpatrick, 1955).)

I shall limit my discussion to some interesting clinical effects of cerebral anoxia which I feel have received less attention than they merit. They fall into two broad groups, namely:

A. Transient or apparently fully reversible effects.

B. Permanent cerebral incapacity of varying degree.

Although experimentally it may be possible to produce cerebral ischæmia independently of anoxia—each showing characteristic histological changes (Hoff *et al.*, 1945)—it is very difficult to envisage cerebral ischæmia occurring clinically without cerebral anoxia. I shall therefore assume throughout that the essential effect of cerebral ischæmia is anoxia and shall not attempt a clinical separation.

A. *Transient or Apparently Fully Reversible States.* (The reservation is made because I have not attempted detailed psychometric testing before and after the event.)

In most of these states the patient is aware, on recovery of full consciousness, that he has been mentally confused—and often in what way. Some of them appear to be of the nature of unduly prolonged, exaggerated and vivid dream-states.

(1) *Sleep-disturbances.*—These take the form of disturbed and restless sleep, nightmares unduly and unusually vivid dreams, and occasionally somnambulism, in patients who have previously not been so disturbed. They occur in patients with heart failure, emphysema and lung failure, and in toxic and febrile conditions.

Case I.—H. L., a man aged 72, had for three weeks suffered from terrifying dreams; he would awaken in the night, panic-stricken, screaming and breathless. His dreams were of different content, but were always vivid, well remembered and terrifying. He had never previously been similarly afflicted. He complained of dyspnœa on effort for the same period but had no cardiac pain. He was in left ventricular failure due to a cardiac infarction. He made a good recovery. A precisely similar series of symptoms occurred sixteen months later. He died suddenly of a coronary thrombosis nearly two years after the first episode. Necropsy showed no notable cerebral abnormality.

(2) *Hypnagogic confusion.*—This occurs quite commonly in healthy people at any age but rarely lasts more than a few minutes. In old people, however, a state of disordered consciousness with loss of contact with reality and mental confusion may last for as long as two hours after half-awakening from sleep and may cause alarm and worry to the patient and to his relations. This state occurs in toxic and febrile conditions, in old people suffering from the effects of cerebral arteriosclerosis and particularly following sleep induced with barbiturates and other potent hypnotic drugs. It probably reflects an undue depression of the respiratory centre during sleep.

The confusion has sometimes been aborted by lobeline or nikethamide given intravenously, when "control" injections of "normal saline" and inhalation of oxygen have failed.

(3) *Iatrogenic confusional states.*—Although such conditions can be permanent and occasionally catastrophic, they are very rarely so (these will be discussed later). But a transient state of mental confusion induced by drugs is extremely common, is often unrecognized and is very frequently treated with the very drugs which produce it!

Case II.—H. B., a man aged 68, was given morphine to alleviate low back pain believed to be due to a vertebral metastasis from prostatic carcinoma. He became a little strange in his manner but still complained of pain and was therefore given more morphine. His mentality rapidly deteriorated; he became aggressive, noisy, difficult to control and doubly incontinent. Over the next twelve hours, morphine, hyoscine and repeated doses of a mixture of chloral hydrate, potassium bromide and opium produced no improvement. He did not recover his normal mental state until twenty-four hours after admission to hospital. He died of uræmia seven weeks later. Necropsy showed no notable cerebral abnormality.

Although the results of bromide intoxication are widely known, far too little attention is paid to the anoxic and histotoxic effects of potent narcotic and analgesic drugs. They readily produce mental confusion in old people and do much to exacerbate any coexisting mental impairment. They should be used with caution and discrimination in old people, and, where sedatives are specifically indicated, drugs such as paraldehyde, chloral or methylpentynol should be tried first.

(4) *Nocturnal confusional states.*—In these there is often delirium, increased motor activity, violent or disordered behaviour and sometimes hallucinosis. Characteristically the patient is mentally quite normal during the day and remembers his mental confusion of the previous night. The disordered behaviour can be so disturbing as to lead to the patient's committal to a mental hospital. When due to lowered cardiac output in heart failure (stagnant anoxia) it frequently responds dramatically to aminophylline given intravenously, but very rarely to oxygen for the arterial oxygen tension is normal. When due to the anoxic anoxia of lung disease immediate treatment is disappointing, but oxygen and lobeline are occasionally helpful. This type of confusion is also seen in toxic, infective, and pyrexial conditions and in uræmia and pyelonephritis.

(5) *Periodic breathing.*—This is a physiological phenomenon during sleep in infancy and is sometimes observed in apparently healthy old people during deep natural sleep. It is seen not infrequently in patients with heart failure, uræmia and chronic anæmias, cerebral arteriopathic conditions, during sleep induced by narcotic drugs and in respiratory and

cerebral disease. It is thought to be due to depression of the respiratory centre and is sometimes associated with lesions of the brain stem. It may be accompanied by fluctuating consciousness and vasomotor disturbances. It usually responds to aminophylline either intravenously or in suppositories. When due to anoxic anoxia and if aminophylline fails, it may respond to oxygen and intravenous lobelline or nikethamide.

(6) *Some other reversible organic cerebral reactions.*—This miscellaneous group is characterized by an apparently completely reversible cerebral reaction including mental confusion, deterioration in personality, intellect and habits, &c., of longer duration than those described above but lasting little longer than the precipitating cause is operative.

Case III.—A. K., a married woman aged 78, suffers from idiopathic aplastic anæmia and has been kept alive for two and a half years by blood transfusions. Whenever her hæmoglobin level falls below 50% (Haldane) she becomes mentally confused, agitated, hallucinated, deluded, incontinent of urine and fæces, and difficult to manage. She is invariably restored to mental normality by blood transfusion. (This case is an example of the effects of cerebral anæmic anoxia.)

Case IV.—E. O., an unmarried woman aged 59, has for many years been crippled with rheumatoid arthritis. She was admitted to hospital with persecutory delusions, incontinence of urine and fæces, noisy, confused and difficult to manage. She was found to be thyrotoxic. Her mental state recovered completely after five weeks of treatment with antithyroid drugs. Two relapses were precipitated by withdrawing treatment and were relieved each time by reinstituting it. Her cerebral condition appeared to be directly related to the degree of thyrotoxicosis as measured by the B.M.R. and radioactive iodine tracer tests. (This appears to be an example of cerebral anoxia due to excessive demand for oxygen by the cells.)

Similar cases occur due to anoxic anoxia in acute bronchitis, bronchopneumonia and other respiratory disorders; and due to both anoxia and histotoxic anoxia, not infrequently, in patients poisoned with hyoscine, barbiturates and other potent hypnotic and analgesic drugs. It is well known, too, that similar transitory confusional states often occur in elderly people following operations under general anæsthesia.

The rapidity with which the organic cerebral reaction due to "cerebral circulatory failure" precipitated by such conditions as acute left ventricular failure, and the hypotensive ("shock") states of coronary thrombosis, acute hæmorrhage and pneumonia can sometimes be reversed is often remarkable: full mental equilibrium has been restored on occasions with the needle still *in situ* during the course of an intravenous injection of aminophylline, a blood transfusion or an infusion of nor-adrenaline. (The rare occurrence of permanent cerebral incapacity associated with these same conditions is discussed later.)

(7) "*Organic neurasthenia*" is a much misused diagnosis which has consequently fallen into disrepute. As defined by Lewis (1947), however, it remains a useful title for a syndrome whose chief features are irritability, languor, fatigue, emotional hypersensitiveness, irascibility, mood disorders, headache, impairment of memory and difficulty in concentration. It occurs as a result of many physical causes, including such anoxic episodes as acute hæmorrhage, operations under general anæsthesia, asphyxia during dental and out-patient nitrous-oxide administration, anoxic pulmonary heart failure, and overdosage with morphine, hyoscine and barbiturates. It tends to recover slowly but completely after the precipitating factor has ceased to operate (Lewis, 1947), but may occasionally be permanent.

(8) *Transient focal neurological signs* (e.g. a rapidly recovering hemiplegia) have been observed in association with conditions causing "cerebral circulatory failure" and are due presumably to "stagnant" anoxia since necropsy has failed to reveal focal cerebral damage. The association of such rapidly reversible cerebral states with the shock of cardiac infarction is well attested (Bean and Read, 1942; Cole and Sugarman, 1952; *Lancet*, 1952). These focal signs are difficult to explain. Possibly there is a coincidental minor cerebral vascular abnormality which escapes detection; the turbulence effect of such an abnormality could well give rise to a pressure drop between the main and subsidiary streams. There are many possible explanations but none which has been proved or which is entirely satisfying.

B. *Permanent Cerebral Incapacity.* The principal groups to be discussed here are the major and minor dementias. In a previous paper (Bedford, 1955) I have reported the occurrence of extreme dementia in 18 previously mentally normal old people following operations under general anæsthesia, while 91 suffered lesser degrees of intellectual impairment. But major and minor degrees of cerebral incapacity following anoxic episodes are by no means limited to old people, nor to operations under general anæsthesia.

(1) "*Organic neurasthenia.*"—Although full recovery is the rule (as has been indicated above) this may be a permanent consequence of cerebral anoxia. The clinical picture merges imperceptibly with that of the lesser degrees of dementia which form the next group. I have no doubt that intellectual deterioration is common to both groups, but in the absence of detailed psychometric testing before and after the event, I have separated them here.

Case V.—H. B. S., a man aged 63, is a retired company director. Four years ago he developed bronchopneumonia and was gravely ill for three weeks, two of which were spent in an oxygen tent, his life despaired of. He made a full physical recovery but since then has been irritable and easily fatigued; he is given to outbursts of irrational anger and weeps uncontrollably at even trivial upsets. He retired three years ago because of his inability to concentrate and has shown no improvement despite faithful adherence to medical advice.

(2) *Minor dementias.*—These comprise minor degrees of impairment of memory, intellect and performance, deterioration in the personality and habits, and lessened emotional control. This clinical picture has been observed following operations under general anæsthesia, dental and out-patient "gas", severe acute hæmorrhage, pneumonia, and overdosage with barbiturates, hyoscine and morphine.

Case VI.—Mrs R. W. N., aged 33, was a vivacious woman, a good conversationalist, and a competition bridge-player. Besides being a competent housewife and the mother of two children, she acted as secretary to her husband—a busy dental surgeon. Five years ago a fingernail was avulsed in the out-patient theatre under general anæsthesia (thiopentone followed by nitrous oxide and oxygen). Recovery was delayed and she was detained in hospital for thirty-six hours. Since then she has been dull and has lost her vivacity. She is forgetful and cannot play bridge. She is faulty at adding up simple sums of money when shopping and is unable to help her husband with his work. She herself says "I don't know what's wrong, but it seems that my mind is foggy—like the 'before taking' picture in the advertisements".

These minor dementias, like the "organic neurasthenias" cause great distress, not only to the patient, but also to his relatives and friends, the tenor of whose complaints is remarkably uniform: "He's just not the same person since . . ." "He's never read a book through since . . ." "She's lost all interest in the family since . . ." "He's never been able to write a decent letter since . . ."

In those of higher intellectual status these minor dementias are even more distressful, and they may be incapacitating to one whose interests and work demand protracted mental effort and concentration; thus the difficulty experienced by a history don in concentrating over a book, and the impairment of memory sustained by a practising surgeon after undergoing prostatectomy, proved so disabling that neither was able to continue his vocation.

The situation is not improved by the misdiagnosis of such cases as "hysteria" and "neurosis" in the young (as was Case VI; and *vide* Cartwright, 1955), and "senility" in the old.

(3) *Extreme dementia.*—This comprises a state in which the deterioration in intellect is so gross that the individual is virtually a human vegetable—unable to help himself, wet and dirty, and mentally inaccessible. Recognizable syndromes within this group include the "decorticate" and "decerebrate" states similar to those following severe head injury. Between this group and the minor dementias there are cases which show intermediate degrees of severity; rarely the Korsakoff syndrome is seen. The clinical patterns are, however, non-specific in the sense that the same picture can be produced by any of the many causes of cerebral anoxia.

I shall attempt only a very simple classification by separating the complex "operation under general anæsthesia" group of cases from those in which a single factor appears to be chiefly operative. Only one case-history will be given in detail for they are all essentially the same in that the patients were mentally quite normal before the episode but abjectly demented following it.

(i) *Extreme dementia following operation under general anæsthesia.*—Of 29 such cases, 18 were operated on while under my supervision so that I was able to compare their mental state before and after operation (Bedford, 1955).

Case VII.—M. S., a woman aged 82, was an intelligent, kindly person—a voracious reader and fond of an argument. She did excellent needlework and was a friendly and helpful neighbour.

While walking in the street she tripped over the kerb and fractured the neck of her right femur. On admission she gave an excellent account of herself. Her hip was pinned under general anæsthesia.

On recovery she was noisy, confused, irrational, incontinent of urine and fæces and mentally inaccessible. She was given sedatives and analgesic drugs with no improvement, but thereafter she slept for long periods. There were no post-operative chest complications; her blood urea, ECG, and blood pressure were normal; there were no abnormal neurological signs. She remained in a state of extreme dementia until her death, three months later, from bronchopneumonia and bedsores. She was doubly incontinent, unaware of her surroundings, and unable to recognize her former intimates.

(ii) *Cerebral circulatory failure* (Corday *et al.*, 1953).—(*a*) *Hæmorrhage:* 5 cases of gross dementia following massive acute hæmorrhage from the intestinal or genito-urinary tract have been recorded (Bedford: to be published).

(*b*) *Hypotensive* ("*shock*") *states:* (i) Cardiac infarction (4 cases); and (ii) pneumonia (4 cases), have precipitated extreme dementia (Bedford: to be published); (iii) severe diarrhœa:

Case VIII.—S. P., a man aged 80, suffered permanent extreme dementia following severe hypotension (B.P. 60/?) lasting for two hours and due to diarrhœa caused by acute salmonella dysentery.

(c) *Cardiac arrest:* (i) During surgical operations on patients young and old.

(ii) In a Stokes-Adams attack:

Case IX.—E. E., a woman aged 78, had for six months suffered infrequent Stokes-Adams attacks due to complete heart block. A period of cardiac asystole lasting six minutes was observed and recorded electrocardiographically. She subsequently recovered consciousness and survived for seventy-two hours in a "decorticate" state.

(iii) *Carbon monoxide poisoning* and *status asthmaticus* need no further mention.

(4) *Localized cerebral damage.*—Transient focal neurological signs associated with the shock of cardiac infarction have already been mentioned. Permanent focal cerebral damage is a well known occasional sequel to anoxic episodes—e.g. Parkinsonism following carbon-monoxide poisoning.

An interesting association which appears to have received little attention in the literature is the occurrence of focal cerebral infarcts in cases of anoxic pulmonary heart disease (cor pulmonale). I have observed 4 such cases (Bedford: to be published):

Case X.—G. C., a man aged 42, had epileptiform convulsions on two occasions during the eighteen months he survived following the diagnosis of congestive heart failure due to chronic bronchitis with emphysema. An executive dysphasia was followed fifteen months later by a left hemiparesis, and both persisted until he died. He had been in sinus cardiac rhythm throughout, and his cerebral vessels were natural at necropsy, yet he had one large infarct in the right hemisphere and several smaller ones in both.

Conclusion.—Although the majority of my examples are drawn from geriatric practice, it must not be assumed that cerebral anoxia is withstood with impunity by younger people. The apparent relative immunity of the young is probably due to their greater "mental reserve" (for they have not yet developed the cerebral circulatory impairment of senescence) and hence to the greater rapidity with which they compensate for any damage they suffer.

A most interesting and puzzling question which emerges from a study of the clinical effects of cerebral anoxia is why they occur so uncommonly. Although very many patients are exposed to serious degrees of anoxia, yet dementia following these episodes is comparatively rare. In an attempt to explain this I have assumed an individual idiosyncrasy—a personal susceptibility—to anoxia in those who suffer cerebral damage. But whether this idiosyncrasy to anoxia is a property of the brain itself, or of the baroceptor reflex mechanisms as has been suggested to me by Dr. Bourne (1955), or of something as yet not defined, I am quite unable to form an opinion. Whatever the cause, however, the risk must be constantly borne in mind. Asphyxia masquerading as anæsthesia; "hypotensive surgery"; the routine (and hence indiscriminate) use of potent hypnotic and analgesic drugs pre-operatively and post-operatively, and in the management of elderly confused patients, are all unjustified. Cerebral anoxia demands immediate relief by urgent removal of the responsible cause.

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Professor A. Meyer (London): *Neuropathological Aspects of Anoxia*

The investigation of anoxia has been one of the major contributions made by neuropathology during the last decades. It would be quite impossible to give an adequate review on this occasion of the numerous important papers which have been published on the subject. In these circumstances, it seems appropriate to confine myself to one type of anoxia for more detailed description and to utilize my experience of other types of anoxia as a background for the discussion of some relevant problems. I have chosen the anoxia due to anæsthesia since there has been, to my knowledge, only one full pathological report of a relevant case in this country (Howkins *et al.*, 1946). Moreover, the subject has gained importance through Bedford's (1955) publication on the effect of anæsthesia in the elderly.

My own experience in death following anæsthesia has been in both human and experimental pathology. The experimental investigations were published with Blume in 1934. The 6 human cases have not yet been published although some have been demonstrated jointly with Dr. Turner McLardy.

TABLE I.—SUMMARY OF FINDINGS IN 6 HUMAN CASES OF DEATH FROM ANÆSTHESIA

Number	Age and sex	Anæsthetic	Arrest	Survival	Cortex	White matter	Striate body	Pallidum	Ammon's horn	Cerebellar cortex	Other subcortical centres
I	54, F.	Ether	Cardiac (15–20 min.)	3 days	+++	−	+++	+−	+++	+++	Thalamus ++
II	46, M.	Ether	Respir, and cardiac (A few min.)	4 days	++	+−	−	−	++	+++	
III	42, M.	N_2O	Respir. (A few min.)	56 hr.	+++	−	+++	+++	+++	+++	Subst. nigra reticulata ++
IV	38, F.	N_2O	Cardiac and respir. (A few min.)	44 hr.	+++	−	+	+	+++	+++	Thalamus ++
V	53, M.	N_2O + Ether	Cardiac (25 min.)	36 hr.	+++	−	+++	+++	++	+++	Thalamus +++ Corpus luysi + Dentate nucleus ++
VI	38, F.	N_2O (Avertin)	Cardiac (1 min.)	6½ mth	+++	+++	+−	+++	+++	++	Thalamus ++ (retrograde degeneration) Dentate nucleus + Amygdaloid nucleus +

Table I gives the main clinical and pathological data of the human cases. There were no major differences between nitrous oxide or ether cases. All cases had cardiac or respiratory arrest or both. There was neither clinically nor at necropsy any conspicuous anomaly which might have been implicated for the respiratory or cardiac complication. The duration of arrest, as far as it is known, ranged from one minute (Case VI) to twenty-five minutes (Case V). While the lesions in Case V were the severest in this series, they are not much less severe in Case VI. In 5 cases the survival was short; Case VI survived six-and-a-half months, in a condition of severe dementia.

On histological examination, severe lesions were seen in all cases in the cerebral cortex, cornu ammonis and cerebellar cortex, while the cerebral white matter was affected in only one case. The striate body and globus pallidus were damaged in most cases, often jointly. The thalamus was severely affected in 3 cases, ignoring the probably retrograde degeneration in Case VI. The reticular zone of the substantia nigra, the corpus luysii and the dentate nucleus were each involved only once. No definite changes were seen in hypothalamus, red nucleus, compact zone of the substantia nigra, geniculate bodies, and the inferior olives. There was, however, in the last case, evidence of an amygdaloid lesion.

I must confine myself to this rather summary description; it is hoped that a full publication of some of these cases will be carried out in due course jointly with my collaborators.

It is interesting to compare these human cases with experimental data in 30 cats (anæsthetized by ether or by ether + CO_2) of which 5 showed irreversible histological changes (Table II). All 5 of these cats had respiratory or cardiac arrest of at least five minutes. All other animals in which no such complete arrest had been effected, showed no significant histological changes. It is of particular interest that the brain of one cat which had suffered a cardiac arrest of as long as ten minutes was histologically normal.

The lesions were similar to those reported in the human cases. The thalamus was not recorded as damaged but the absence in the list of this centre and of other subcortical centres may be due to the lack of attention on our part to these areas; the slide material is unfortunately no longer available for fuller study.

TABLE II.—SUMMARY OF FINDINGS IN 5 CATS SUBMITTED TO ANÆSTHESIA (MEYER AND BLUME, 1934)

Cats	Anæsthetic	Arrest	Survival	Cortex	White matter	Striate body	Pallidum	Ammon's horn	Cerebellar cortex	Other subcortical centres
1	Ether	Respir. and cardiac (10 min.)	4 days	+++	−	++	++	+++	++	Subst. nigra reticulata+
2	Ether	Respir. (10 min.)	6 days	++	+	++	−	+	++	
3	Ether	Respir. and cardiac (5 min.)	6 days	++	+	−	+++	+	−	
4	Ether and CO_2	Respir. (10 min.)	8 days	−	−	−	+	+	−	
5	Ether and CO_2	Respir. (18 min.)	3 days	−	++	+++	++	++	++	

DISCUSSION

In all human and experimental cases with irreversible pathological lesions, cardiac or respiratory failure had invariably occurred. The experimental series is particularly informative, as it shows that none of the animals without respiratory or cardiac stoppage showed any appreciable histological change. In Bedford's recently published cases, no complete arrest seems to have occurred although considerable hypotension was described in at least two. However, none of our cases belonged to the category of the elderly; it might well be that in the elderly lesser disturbances of the circulation and respiration may suffice to produce irreversible lesions resulting in dementia. Unfortunately, in none of Bedford's cases is the histology given because of the difficulty of distinguishing between post-anoxic and senile vascular lesions. Although this may be true in some cases, I believe that it is often possible to identify anoxic lesions by the combination of cortical or—alternatively—white matter lesions with cerebellar and basal ganglia lesions. In view of the practical and theoretical importance of this material it would be most valuable if, in spite of the difficulties, all cases of the elderly suspected of death from anæsthesia, should be submitted to full neurohistological investigation.

The lesions in almost all human and experimental cases were severe and widely distributed. They would indeed account for the dementias which have been described after anæsthesia and other types of anoxia including irreversible hypoglycæmic coma and carbon monoxide poisoning. The dementias produced in this way may be so profound as to give rise to an erroneous diagnosis of protracted coma or hysterical pseudodementia. On the other hand, cases with strictly localized brain damage do occur; in a fully investigated case of carbon monoxide poisoning, unilateral softening of the globus pallidus was the only lesion we found. Likewise, bilateral softening of the reticular zone of the substantia nigra was in one dog the only appreciable histological effect of experimental cyanide poisoning (Meyer, 1933).

In general, the localization of the lesions in our human and experimental post-anæsthetic cases falls into line with the observations made by many workers in various types of anoxia. There are some as yet unexplained differences in detail: the globus pallidus seems to be more often selectively affected in carbon monoxide poisoning than in any other type of anoxia. Involvement of the globus pallidus is practically unknown in irreversible hypoglycæmic coma, although striatal lesions are quite common, and this is also the case in epileptic brains despite frequent sclerosis of the cornu ammonis.

The thalamus, apart from its occasional involvement in epileptic brains (Scholz, 1951), has not figured prominently among the vulnerable centres in anoxia. The severe necrosis in this area in three of the human cases described in this paper deserves, therefore, special mention. Fig. 1 demonstrates the lesion in Case V. In this case, the acute necrosis was almost total except for some sparing of the reticular, intralaminary and midline nuclei. There was an equally total necrosis of the striate body extending even into the claustrum. We have observed thalamic necrosis also in other types of anoxia. In a case of delayed death after hanging with survival of three days, for instance, putamen and globus pallidus showed only minimal damage, while the thalamus was severely necrosed, again with distinct sparing of reticular, intralaminary and mid-line nuclei (Fig. 2). There was, in this case, together with other typical lesions, a necrosis of the latero-basal aspect of the amygdaloid nucleus (Fig. 2). This is of interest, in the light of recent findings in epileptic brains, in which sclerosis of this centre has been reported to be associated with that of Ammon's horn (Meyer and Beck, 1955).

The reticular zone of the substantia nigra has been found damaged in some of our human and experimental postanæsthetic cases. Similar findings have been recorded after carbon monoxide and cyanide poisoning. Although the reticular zone is both anatomically and histochemically closely related to the globus pallidus, the incidence of its necrosis is much lower than that of the globus pallidus. Nevertheless, in one case of experimental cyanide

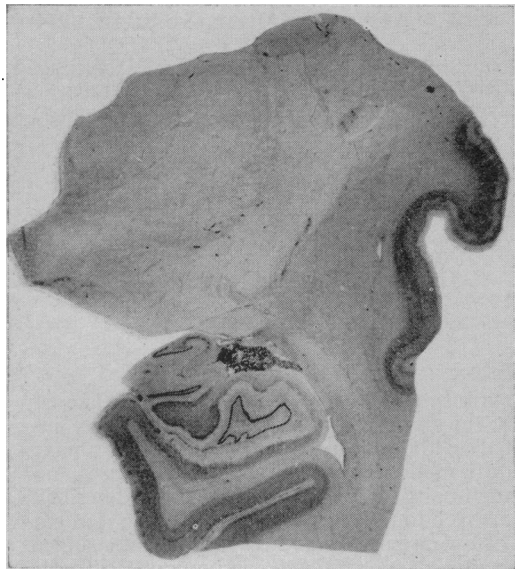

FIG. 1.—Case V of Table I. Ischæmic necrosis of thalamus, striate body and claustrum. Insula shows laminary necrosis of third layer, otherwise normal staining. Nissl stain. × 2.

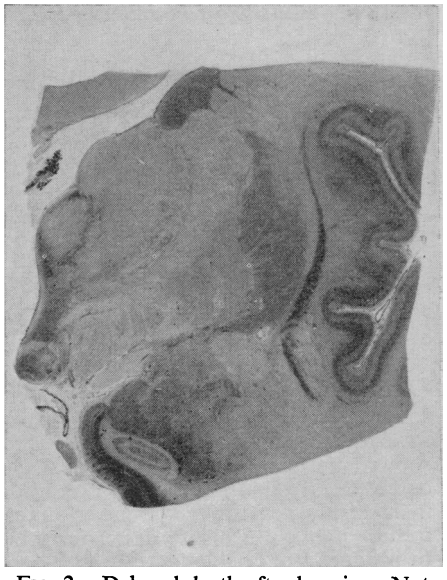

FIG. 2.—Delayed death after hanging. Note thalamic necrosis; the striate body stains in the normal manner, apart from focal necrosis. Laminary necrosis of third layer in insula. Necrosis of latero-basal part of amygdaloid nucleus. Nissl stain. × 1·5.

poisoning a bilateral selective softening of the reticular zone was the only important change in the brain (Meyer, 1933). In two similarly poisoned carnivores, on the other hand, a bilateral softening of the globus pallidus was noticed, entirely sparing the reticular zone.

These facts emphasize the complexity of the problem. If there is a pattern of selective vulnerability to anoxia, it is likely to depend not on one but several factors which may vary not only with different types, but occasionally in an almost freakish manner, even within the same type of anoxia. The direct effect of oxygen-want upon the nervous tissue is probably one important factor. Others arise from the repercussion of oxygen-want upon the circulation resulting—to varying degrees—in capillary and venous stasis, increased permeability of vessel walls, œdema and raised intracranial pressure. Increased cerebral activity at the critical period, as it occurs in states of motor excitement or in epileptic discharges, may also have a determining influence upon the site of lesions.

The latest contribution to the problem of selective vulnerability has been made by Lindenberg (1955), who, from experience in head injuries, is inclined to explain most of the selective lesions by the local pressure which some arterial systems undergo during conditions of increased intracranial pressure. Arteries running close to the tentorial edge (such as the anterior choroidal, posterior cerebral, and superior cerebellar) or which may be pressed against the falx (branches of anterior cerebral) or bone (the stem of the middle cerebral, inferior cerebellar arteries, &c.) are particularly exposed. All terminal branches which supply cerebral or cerebellar cortex in the depths of sulci are similarly vulnerable. Lindenberg's views fall into line with the herniation theory of Earle *et al.* (1953), in temporal lobe epilepsy, and, to some extent at least, with views expressed by the present writer and his associates (Meyer, 1939; Meyer *et al.*, 1954; Meyer *et al.*, 1955). Although a detailed critical assessment of Lindenberg's paper must be reserved for a later occasion, it undoubtedly deserves close attention in the further discussion of this difficult problem.

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