food factors consumed may fall to dangerously low levels. The development of "meals on wheels" services provides an opportunity of supplying a meal which is not bulky and unappetizing to the elderly and is rich in the nutrients mentioned above. It must also be easy to masticate. The design of such meals constitutes a special problem in dietetics.

Elderly people are often loath to consult the doctor for conditions which are not painful and do not disable them. Quite often they believe that these are the inevitable concomitants of old age. Even among doctors there is sometimes found an unnecessarily fatalistic attitude.

In this survey the frequency of symptoms of untreated prolapse in the women suggested that some of these patients might have benefited, perhaps many years before, from attendance at post-natal clinics and from active gynaecological treatment. Similarly, with the men, there were a fair number with hernia whose condition would have been improved by an operation or a properly fitting truss.

Much of the disability of old age due to failure of eyesight and hearing can be ameliorated by the provision of suitable spectacles, by ophthalmic operations for such conditions as cataract, and by hearing-aids.

It has been noted that foot troubles were a common cause of disability. Many old people would benefit from the services of a chiropodist and advice on the care of the feet.

Routine Medical Examinations

The discovery, in the course of the survey, of several cases of unsuspected serious and treatable disease has already been mentioned. This suggests that certain specified routine examinations of the elderly aimed at early diagnosis are worth considering. A simple set of tests consisting of an examination of the urine for sugar, a haemoglobin estimation, inspection for evidence of myxoedema and carcinoma of the skin, and weighing, would detect most cases of diabetes, anaemia, myxoedema, carcinoma of the skin, obesity, and loss of weight. A test of visual acuity and hearing might also be included. Such a routine examination should be feasible in the general practitioner's surgery or even in the patient's home, and would lead to the earlier diagnosis of some important and common conditions in the elderly. It might, on the other hand, be appropriate for the local health authority to organize such a service as a preventive measure.

Summary

This paper describes the general results of a survey which was carried out in Sheffield in the years 1949-51. The aims of the survey were to investigate and describe the state of health and the diets of elderly people living at home in Sheffield; to examine the relationship between health and such factors as age, sex, marital state, social class, and diet, and to collect information on normal physiological standards in the elderly.

A good deal of previously undiagnosed illness and disability was discovered for which treatment was required.

Specific suggestions are made for the prevention of disease and disability in the elderly.

The survey was made possible by a generous grant from the Nuffield Foundation. Dr. H. Droller carried out the clinical examinations and Mr. D. L. Woodhouse organized the field work and collected social data. Miss Cissie Roseman undertook the statistical analysis. Dr. E. R. Bransby, of the Ministry of Health, was responsible for the organization and analysis of the dietary survey. Dr. E. G. Mackie, Dr. J. L. A. Grout, Professor G. L. Roberts, Dr. A. Jordan, Dr. J. Colquhoun, and Dr. E. K. Blackburn organized the ophthalmological, radiological, dental, biochemical, and haematological examinations at the Royal Hospital, Sheffield, and Mr. J. F. V. Larway carried out the photography. To all of these, and to many other associates

too numerous to mention by name, including many general practitioners, our thanks are due; and also to the 476 elderly people of Sheffield who by their patient co-operation made this survey possible.

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CEREBRAL HYPOXIA: AETIOLOGY AND TREATMENT

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The therapeutic value of dehydration therapy following an acute hypoxic episode has been demonstrated in cases of cardiac arrest by Sadove *et al.* (1953). They suggest that once the heart has been restarted and an adequate oxygen supply to the brain ensured, an active regimen should be instituted to combat the cerebral oedema which occurs, and which is a direct result of hypoxic damage to the cerebral capillaries. Seldon *et al.* (1949), Lucas (1950), and Cole (1951) have also considered this hypothesis and instituted dehydration therapy.

We would stress, however, that this syndrome of cerebral oedema also occurs in instances other than that of cardiac arrest and that any case showing signs of cerebral damage after a period of cerebral hypoxia may be adequately and gratifyingly treated by means of dehydration therapy. The supply of oxygen to the brain is of paramount importance, and it may not be realized that gradual deprivation of the oxygen supply by any means may lead to the onset of cerebral oedema. Examples of some of the clinical conditions which may produce hypoxia to a degree sufficient to cause cerebral oedema are shown in the diagrammatic Table.

The immediate effect of hypoxia is to produce a vascular dilatation (Courville, 1947). The vessels may be so damaged that small haemorrhages occur from rupture of their walls; in areas less severely damaged there is interference in their normal permeability, and cerebral oedema is produced. Should this oedema not be treated, progressive damage to the brain may continue for a long

Examples of Clinical Conditions which may Lead to Cerebral Hypoxia and Oedema

ANOXIA OR HYPOXIA			
ANOXIC	ANAEMIC	STAGNANT	HISTIOTOXIC
During Operation: Low Oxygen % mixture Badly administered N ₂ O Acute or Chronic respiratory obstruction; e.g., Laryngeal spasm Inhalation of vomit Complications during thoracic operations, etc. Prolonged respiratory arrest Severe bronchospasm	Chronic anaemia plus Another factor Haemorrhage: Traumatic Operative Post-operative Carbon monoxide poisoning	Cardiac arrest Shock: Traumatic Surgical Post-operative Hypotension from too prolonged or drastic use of 1. Arteriotomy 2. Hexamethonium 3. High spinal	Anaesthetic overdose
Post-operative: Respiratory obstruction Massive collapse of lung Inhalation of blood, vomit Partial curarization			
Other conditions: Anoxic attack in Fallot's tetrad Acute respiratory obstruction, e.g., Laryngeal oedema Carc. of larynx Haem. into thyroid cyst, etc. Pneumonia, bronchopneumonia Paralytic poliomyelitis Asphyxia neonatorum following foetal distress Barbiturate poisoning			
HYPOXIC CEREBRAL DAMAGE and CEREBRAL OEDEMA			

period of time, and cells "reversibly" damaged during the acute episode may become irreversibly damaged even though the oxygen supply has been restored.

Forbes *et al.* (1924), Yant *et al.* (1934), Chornyak (1938), and Windle and Becker (1943) have produced evidence that the subsection of the brain to periods of hypoxia will produce cerebral oedema. Hypoxia in the first instance causes an increase in capillary permeability which permits the passage of protein into the extravascular spaces, with consequent rise in the extracellular osmotic pressure; fluid is drawn out of the vessels and a cerebral oedema is produced. This now acts as a physical barrier interfering with oxygenation of the partially damaged brain cells; in addition it raises the cerebrospinal fluid pressure and venous obstruction is encouraged, each of which acts to the detriment of the cerebral circulation and the chances of cellular recovery. Further hypoxic damage occurs and a vicious circle

FIG. 1.—Vicious circle of cerebral hypoxia.

becomes established (Fig. 1). The chances of "vegetabilization" and death are now great. Thus it will be seen that the institution of dehydration therapy, in any case where there has been a period of hypoxia severe enough to allow the condition to arise, is reasonable, and will, where the cerebral oedema is already developing or established, tend to break the vicious circle.

Clinical Appearance of Cerebral Oedema

Patients who are suffering from cerebral oedema present a complex clinical picture. Signs of cerebral damage

depend upon the depth of coma and thus to some degree on the duration and severity of the hypoxia. There will be a history of an anoxic or a hypoxic episode, from which a partial recovery has been made. This recovery may in some instances have been complete but a relapse has occurred later on. The patient is comatose, with stertorous or gasping respiration, and commonly a marked tracheal tug is noted. The temperature is raised up to levels of 105° F. (40.6° C.) quite early on and sweating of the face and neck is pronounced. The pupils are usually dilated, but may be constricted; they are equal, and a coarse nystagmus may be present. Some patients will be restless, with twitching movements of the limbs and even choreoathetosis, with fits occurring in the later stages.

The signs of recovery may be dramatic, but a generalized lightening of the depth of the coma, with a return of voluntary movements, increased restlessness, and a response to painful stimuli, is encouraging. The respiratory rhythm returns to normal and the raised temperature falls.

The terminal picture of the condition is shown by a deepening of the coma, an increase in pulse rate, and the development of Cheyne-Stokes respiration. Flaccidity and loss of deep reflexes occur, and with the patient in a hyperthermic state death ensues.

Patients who do not die from the effect of hypoxia may nevertheless suffer permanent cerebral damage which manifests itself by mental and emotional aberrations, by motor disturbances such as hemiparesis, athetosis, and incontinence, and by defects of vision. Two such pathetic cases are described by Polani and MacKeith (1954) and others by Courville (1947) and Bedford (1955).

In a post-operative case cerebral oedema must be distinguished from conditions such as carbon dioxide retention and partial curarization following anaesthesia, but the presence of a hypoxic episode will usually exclude these phenomena. Cerebral oedema due to hypoxia may, however, be superimposed upon both these conditions.

Dehydrating Agents

Dehydrating agents act by their physical property of increasing the crystalloid osmotic pressure of the plasma; water is consequently drawn into the circulation from the interstitial fluid, and intracellular fluid, in its turn, passes into the extracellular spaces. A final osmotic equilibrium between the plasma and interstitial fluids is reached, both being slightly hypertonic and with an increased volume, so the dehydrating effect is transient. This stage would be harmful if it were not for renal activity. Factors enhancing the effectiveness of the dehydration are the rapidity of metabolism and the speed of excretion of the agent, the presence of a diuresis, and the restriction of fluid intake. A "rebound" wave of high pressure occurs when hypertonic solutions which are stored in the tissues are used.

Glucose (50%), as well as being such a substance, also passes through the arachnoid membrane, causing a rise of the osmotic pressure of the cerebrospinal fluid, which therefore works in the reverse direction to that required (Gregersen and Wright, 1935).

Sodium chloride (30%) causes a greater reduction in C.S.F. pressure, but also a greater reaction (Milles and Hurwitz, 1932). Weed and McKibben (1919) found that it was toxic and led to cardiac and respiratory disturbances.

Sucrose (50%) is our preference as the initial drug to use for the treatment of generalized cerebral oedema due to hypoxia. It does not pass through into the C.S.F., so no rise of osmotic pressure in that fluid occurs (Reid, 1943; Gregersen and Wright, 1935), it is not stored in the tissues like sodium chloride or gradually metabolized like glucose,

but in man it is almost completely excreted by the kidneys (Power and Keith, 1936), and, acting thus, like urea, produces a marked diuresis amounting to four times the quantity injected (Jackson *et al.*, 1937). This diuretic quality is important, for rebound oedema is avoided, dehydration is assisted, and kidney function is maintained during this critical period.

Sucrose is alleged to cause renal damage, but the evidence for this is conflicting. Anderson and Bethea (1940) found changes such as swelling and granularity of the cytoplasm of cells lining the convoluted tubules in mild cases, and nuclear shrinkage and pyknosis in severe ones. However, it should be noted that all these patients had previous renal damage, and doses of 1,000–3,350 ml. were injected over four days. Lindberg *et al.* (1939) gave 200 ml. of sucrose intravenously in a single dose to 15 patients; none of these showed any impairment of renal function and their urea clearance was essentially unchanged. However, some changes were noticed in dogs that were given prolonged daily or repetitive injections. Feher *et al.* (1942) conclude that sucrose is safe, provided there is no pre-existing renal or cardiac disease. For these reasons once the initial dehydration period is over we continue treatment with another agent, 10% dextran being our preference.

Concentrated human serum is suggested by Lucas (1950) and Cole (1951); Seldon *et al.* (1949) used 25% serum albumin; Sadove *et al.* (1953) suggest double- or quadruple-strength plasma on account of its ready availability, but against this must be weighed the risk of serum jaundice.

Treatment

Our routine, once a diagnosis of cerebral hypoxia and oedema has been made, is to administer 40 ml. of 50% sucrose intravenously and to wait 15 minutes to assess its result. According to the severity of the hypoxia so will the effects of the sucrose vary. Sometimes an immediate return to consciousness will occur. The majority of patients will not show such a dramatic response, but if the diagnosis of cerebral oedema is correct some lightening of coma and other evidence of recovery should be seen.

After 15 minutes a further 40 ml. of 50% sucrose should be given, followed in 30 minutes by another 20–40 ml., according to the response of the patient. After this an intravenous 10% dextran drip is set up and allowed to run

at about 50 ml. an hour. This latter may be unnecessary, and judgment must be made according to the patient's progress: any falling off in recovery will indicate the need for more prolonged treatment.

A good response in the patient's condition must not make one forget that all the tissues have been equally insulted by the anoxia or hypoxia, and care must be taken that an upright position is not adopted too quickly or severe cardiovascular collapse will occur. In patients who, although better, are still comatose, Sadove *et al.* (1953) recommend a slight head-down tilt at approximately 7 degrees as being ideal for drainage of secretions without causing congestion of the brain. Additional treatment—consisting of adequate airway and oxygenation, prevention of acute dilatation of the stomach, maintenance of blood pressure, restriction of fluids, and administration of antibiotics—is fully dealt with in their paper.

Three case histories are presented to illustrate the scope of this treatment.

Case 1. Anoxic Episode in Fallot's Tetralogy

In October, 1953, a 6-year-old girl suffering from Fallot's tetralogy had two angiocardigrams carried out under general anaesthesia; the diadone injections were uneventful and there was no evidence of shock or reactions.

(A) At 5.20 p.m., two hours after returning to the ward, and while sleeping off the effects of her anaesthetic, she had some form of anoxic attack which resulted in her becoming very shocked and cyanosed. There was generalized bronchospasm and shivering, and her limbs became rigid and spastic. Theophylline with ethylenediamine ("cardophyllin"), 0.12 g., was given intravenously, with some improvement in the circulation, and the blood pressure rose to 100 mm. Hg (Fig. 2).

(B) The improvement was not maintained, and two further injections of theophylline with ethylenediamine were given with greater, and maintained, improvement in the circulation. However, the patient was still unconscious and unresponsive to painful stimuli; an injection of sucrose was discussed, but it was decided to wait a bit longer before giving it, as our experience at that time was so small and the child was so ill.

(C) A small quantity of fluid was vomited and sucked out: the level of consciousness was unaltered.

(D) In view of this and also the great rise in pulse rate, and particularly the increase in temperature to 105° F. (40.6° C.) and her general deterioration, we injected 11 ml. of 50% sucrose intravenously; there was at once a great improvement in her general condition and the level of consciousness, and the child responded to painful stimuli.

(E) The temperature remained at 105° F. (40.6° C.), and a further injection of 11 ml. of sucrose was given, which resulted in semiconsciousness, talking, and much more generalized response to painful stimuli.

(F) The temperature was subsiding, but in view of the pulse rate increasing again to 200 a minute a third injection of 11 ml. of sucrose was given just over an hour later. This resulted in the child answering simple questions; she moved spontaneously and gave a strong cough. Her colour was almost normal.

FIG. 2.—Case 1. Chart of a 6-year-old child following angiocardigraphy.

(G) General improvement continued, and by 3 a.m. she was quite conscious and asking for a drink; her limbs moved normally and her temperature was down to 100° F. (37.8° C.); pulse rate 130. At 8 a.m. she was so well that she appeared as any other child who has had angiocardio-graphy performed on the previous day, and there was no evidence then or later of any cerebral damage.

Case 2. Post-operative Respiratory Obstruction

On October 20, 1954, a 50-year-old man had an oesophagectomy performed. The seven-hour anaesthesia and operation were uneventful and 2 pints (1,140 ml.) of blood was transfused. While awaiting return to the ward he became obstructed and cyanosed. The airway was regained, and his condition appeared satisfactory on return to the ward; about an hour later he had a severe anoxic episode and circulatory collapse. During the next two hours he had two further anoxic attacks due to cessation of respiration, but responded to resuscitatory measures.

Seven hours after the operation he had still not recovered consciousness and his blood pressure was falling (Fig. 3). One pint (570 ml.) of blood was rapidly transfused without obvious benefit. He was still comatose, the pupils were dilated, the eyes were rotating, the upper limbs were twitching and he made feeble plucking movements at the bed-clothes. Cerebral hypoxia was diagnosed and 30 ml. of 50% sucrose was injected. A further 20 ml. half an hour later resulted in a good response; consciousness was regained, and the patient coughed, moved spontaneously, and swallowed his secretions well. Within half an hour slight deterioration occurred, but after another 30 ml. of sucrose he spoke coherently and asked for a drink "over there on the table." His head was raised on two pillows.

Shortly after this he had a very sudden complete collapse, with respiratory arrest and an impalpable pulse. Respiration was controlled with 100% oxygen; the foot of the bed was raised, and his colour returned in about four minutes. He remained in coma with a weak and irregular pulse. A sucrose drip was set up and 60 ml. of 50% sucrose was run in; he regained consciousness and was talking again. The drip was continued with 10% dextran, and during the next six hours one pint (570 ml.) was transfused. Gradual circulatory improvement occurred during this time.

When seen at 8 o'clock next morning he looked well and was sitting up in bed. He appeared quite as fit as a patient could normally be expected to look on the first day after oesophagectomy. He said he felt well and had no recollection of the previous night's happenings. His B.P. was 110/70; pulse 120. A total quantity of 1½ litres of urine had been passed at 2 a.m., 3 a.m., and 9 a.m.

Case 3. Pyrexia in Severe Anaemia

A woman aged 47 was originally admitted in October, 1953, with a diagnosis of ruptured tubo-ovarian abscess and generalized peritonitis. Emergency laparotomy confirmed this diagnosis; the abscess was drained and a colostomy performed. She was subsequently discharged to convalescence with a temporary colostomy, and was to return to the out-patient department in one month for reassessment and subsequent closure of the colostomy. She failed to attend, however, and we lost track of her until 10 months later. At that time she had been in bed for four months. She was getting much weaker, and had had little or no food for some weeks. A relative who had been looking after her stated that she was becoming more confused.

On examination she was clinically anaemic; temperature 101.6° F. (38.7° C.), pulse 120, blood pressure 120/80. She was stuporous but responded to stimuli, both plantar responses were downwards, the disks were clear, and no other objective signs, apart from a large mass in the pelvis, were found. The haemoglobin was 5.6 g. per 100 ml. (38%).

She was given 4 pints (2,270 ml.) of blood, 2 pints (1,140 ml.) of "casydrol," and ½ pint (280 ml.) of K/Na mixture. Her condition, however, gradually deteriorated, and the coma deepened until she no longer responded to stimuli. Choreo-athetotic movements of the hands became persistent, and the pupils were equal and reacted to light.

Laparotomy was decided upon, and in view of the possibility of cerebral oedema being present 40 ml. of 50% sucrose was given. Recovery, though not dramatic, was encouraging, and anaesthesia was induced with cyclopropane and oxygen. Laparotomy revealed massive carcinomatosis and the abdomen was therefore closed. A further 40 ml. of 50% sucrose was given with considerable benefit. Return to consciousness was rapid and her general condition improved. Within six hours her nervous state was normal and no evidence of mental confusion could be determined within 12 hours.

This case appeared to be one in which hyperpyrexia with consequent rise in basal metabolic rate and oxygen consumption coupled with a severe chronic anaemia had initiated the onset of cerebral oedema. In addition, hyperpyrexia gives an increase in the water content of cerebral, cerebellar, and brain-stem grey matter (Wyatt and Pilcher, 1951).

Some of the other cases we have treated have had cerebral hypoxia due to the inhalation of vomit during anaesthesia in acute eclampsia; acute respiratory obstruction during laryngoscopy in a patient who had had a chronic obstruction due to carcinoma of the larynx; prolonged hypotension due to severe shock; severe prolonged hypotension and coma due to peritonitis from a perforated Meckel's diverticulum during labour; and asphyxia neonatorum following severe foetal distress.

FIG. 3.—Post-operative chart of Case 2. The black squares at the top indicate anoxic attacks.

Discussion of Treatment

Although our experience in the treatment of these cases of hypoxia from various causes is limited, we have been impressed with the results which we have seen, and feel that its use should be extended and that it would benefit patients who have had a less severe and dramatic episode than cardiac arrest, and also those who have had two subliminal, as it were, hypoxic states and in whom the diagnosis of cerebral hypoxia is often not obvious owing to the insidiousness of its onset. Histological evidence confirms that such treatment would be rational.

Anoxic anoxia from any cause, if severe or prolonged, will give rise to cerebral oedema, and this was shown histologically by Yant *et al.* (1934) in dogs killed after breathing a mixture deficient in oxygen. The appearances were quite similar to carbon monoxide poisoning, and the conclusion was that these parenchymal changes may be due to the direct effect of the anoxia and also the secondary effects of a disturbed blood supply.

The histopathology is predominantly one of vascular dilatation, stasis of the entire capillary system, and perivascular haemorrhages. Yant *et al.* (1934) found severe perivascular and perineuronal oedema especially involving the cortex, corpus striatum, and dorsal nucleus of the vagus. In slow carbon monoxide poisoning the oedema was so severe that the medulla had a mesh-like appearance and the stasis, filling, and dilatation of the small vessels were such as to make it appear like an artificially injected specimen. Forbes *et al.* (1924) studied dog brains through a trephine hole and noted that the main brain swelling occurred, not in the acute asphyxial stage, but in the recovery stage—that is, owing to oedema. They described a case of carbon monoxide poisoning in which 100 ml. of 15% NaCl was given intravenously with good results. We are unable to find any other reference to the treatment of carbon monoxide poisoning by dehydration, and although we have not had an opportunity of managing a case we feel sure that it should respond most favourably.

There is ample evidence that the residual coma or neurological sequelae after nitrous oxide are due not to an inherent toxicity of nitrous oxide, but to the concomitant hypoxia which must occur if attempts are made to produce too great a depth of anaesthesia. Courville (1939) states that the degree and extent of the ultimate cerebral damage is proportional to the insult to that particular area during hypoxia. In addition to the anoxic cellular changes he found marked enlargement of the perivascular and perineuronal spaces, giving the appearance of oedema. The cases described in Courville's monograph mostly had nitrous oxide anaesthesia alone and probably secondary saturation, but even to-day cases are reported following dental anaesthetics in which a hypoxia insult had doubtless been administered (Bourne, 1955).

Chornyak (1938) studied the brains and lungs of monkeys given pneumonia experimentally; at necropsy he found a direct relationship between the amount of brain damage and the degree of lung involvement. He also studied brains of patients dying of pneumonia or bronchopneumonia, and similarly found an accurate correlation of lung and brain damage. The picture was similar to that of oxygen-deficient atmospheres and carbon monoxide poisoning—the vascular reaction being hyperaemia, stasis, oedema, diapedesis, endothelial reaction, and areas of disintegration of the capillary wall.

Although it is now rare to get such large areas involved in pneumonic consolidation, cerebral hypoxia may occur if, in addition, the patient has a cyanotic congenital heart lesion, anaemia, or other factor affecting the mechanism of oxygenation.

Infants suffering from asphyxia neonatorum show findings, including oedema, similar to other causes of cerebral anoxia (Schreiber, 1938; Windle and Becker, 1943). It is always

difficult to eliminate a tentorial tear or haemorrhage as the cause of the asphyxia, but, if the child's asphyxia appears to be due to foetal distress or maternal anoxia prior to delivery, sucrose may play a part in addition to the routine treatment for this condition.

Cardiac arrest is the condition which originally stimulated interest in this method of therapy. Our knowledge of its treatment has been advanced with the increasing severity of the cardiac manipulations now performed, and the use of 50% sucrose in any case in which the circulation has been inefficient for any length of time has become our routine.

Ventricular fibrillation may be seen occasionally in almost any kind of direct operative procedure upon the heart, and the restoration of an efficient rhythm may take some time. Although the patient will be receiving pure oxygen, the colour deteriorates even with good cardiac massage, and the congestion and cyanosis in the face are most striking. In those cases which have failed to respond to treatment the necropsy findings in the brain are suggestive of the presence of oedema, though difficulties with histopathological techniques and the changes due to autolysis make post-mortem examinations unreliable.

Bedford (1955) commented upon the personality changes following anoxic episodes. We have not been able to draw any conclusion about these in our cases, since all our patients who have suffered any form of anoxia now receive 50% sucrose as a routine.

One of these patients, a man aged 54, was operated upon for aortic stenosis. The manipulation of his heart caused it to fibrillate, and it returned to normal rhythm after 22 minutes. During this time there was no doubt that he suffered considerable cerebral anoxia although cardiac massage was being performed. Whilst he was waiting to return to the ward he had a sudden haemorrhage of some four to five pints (2,270 to 2,840 ml.) into the chest, which was therefore reopened. The bleeding-point was secured, but he developed a further attack of ventricular fibrillation, which persisted for a period of 45 minutes before normal rhythm was eventually restored, and again the persistent cyanosis and congestion gave evidence of an inefficient cerebral circulation. He was given 50% sucrose and made an uneventful recovery. According to his relatives no personality changes are apparent—a fact which confirms our own impression.

Other conditions in which generalized cerebral oedema is said to occur are hypoglycaemia, barbiturate poisoning, suicidal hangings, and heatstroke (Hoff *et al.*, 1945).

The localized oedema that occurs around brain tumours, abscesses, and head injuries is thought to be due to local toxic metabolites, to ischaemia from venous congestion, to a peculiarity in the osmotic pressure in capillaries around the tumour, or to increased permeability in these capillaries, and to inflammatory oedema in the case of abscesses (Greenfield, 1947; Jefferson, 1947).

Whatever the cause of the oedema, dehydration therapy is of only very temporary and negligible use, as of course the causative factor is still present and selective dehydration of localized oedema is not practicable.

It must be emphasized that dehydration therapy will be valueless if used in any case of undiagnosed coma. However, it has proved so effective in patients in whom there has been a definite hypoxic episode that we have on occasion administered 50% sucrose to cases in which there has been only strong presumptive evidence of hypoxia. It is considered that 50 ml. would be harmless even though no oedema were present, and a lightening of the coma would render the diagnosis certain and enable energetic treatment to be pursued.

It will be appreciated that no histological evidence is available for the successful cases that we have described, but we are carrying out work on experimental animals which we hope will demonstrate conclusively the beneficial result of dehydration therapy following a hypoxic episode.

Summary

The appearance of cerebral oedema following hypoxic episodes is described; its incidence appears to be more common than hitherto realized and may follow cerebral hypoxia from a variety of causes.

Dehydration therapy with 50% sucrose followed by 10% dextran is described: favourable results have been obtained from its use.

Some successful cases are reported.

The wider application of dehydration therapy is suggested; histopathological reports from the literature confirm that this would be rational.

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The Report of the Work of the London School of Hygiene and Tropical Medicine for the Year 1954-5 has recently been published. Considering the problem of the ethics of clinical trials, the report from the department of medical statistics and epidemiology stresses that experimental requirements are always subservient to the consideration of whether a treatment, beneficial but unproved, can be withheld from a patient, or "dummy" treatment given. Sometimes the length of a trial is not determined beforehand so that it can be stopped if significant differences appear in the results, though this may impose serious limitations on the researcher. Among new studies undertaken during the year the Ross Institute of Tropical Hygiene has for the first time opened research into the resistance of anophelines to insecticides as part of the world-wide drive against malaria, strongly supported by the recent World Health Assembly. The new concept of the total elimination of malaria wherever feasible ensures that the disease is likely "to take a large part of the interest of people concerned in tropical hygiene." The future policy of the school for 1957-62 must be submitted to the university at the end of the year. The one respect in which the school is cancelling development plans is at Winches Farm, used for breeding laboratory animals. In atomic warfare a wartime base so near to London would be valueless.

ANTIGENICITY STUDIES ON SALK-
TYPE POLIOMYELITIS VACCINE

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The recent report from the United States Poliomyelitis Vaccine Evaluation Center (Francis *et al.*, 1955) on the efficacy of vaccine used in the 1954 field trials has encouraged hopes that effective control of paralytic poliomyelitis is now at hand. In early 1955 pilot quantities of vaccine were prepared in the United Kingdom. In May it was decided that the vaccine should not be used because it was prepared from the Mahoney Type 1 virus. However, one vaccine batch had already been used in a small number of human volunteers in the Sheffield area, and it is therefore of interest to compare the human response to immunization with the results of potency tests carried out previously on laboratory animals.

Technical Methods

Vaccine Preparation

In general, the methods used were similar to those of U.S. manufacturers, as outlined in the "Minimum Requirements for Poliomyelitis Vaccine" issued by the National Institutes of Health. Types 1, 2, and 3 poliomyelitis viruses were represented by strains Mahoney, MEF-1, and Saukett, respectively. Virus strains were propagated in large tissue cultures of kidney tissue from the rhesus monkey. After filtration, "strain pools" were inactivated with 1:4,000 formalin at 37° C. The trivalent preparation was formed by combining the inactivated single-strain pools in approximately equal quantities. Safety tests were carried out in tissue culture and on monkeys, and no active virus was detected. Merthiolate 1:10,000 was added as preservative. All potency tests were performed within four months of the date of manufacture.

Immunization Schedules

(i) *Mice*.—Mice in two groups of 40 were each given three injections of 0.5 ml. intraperitoneally at weekly intervals. For one group the vaccine was employed undiluted, for the other it was diluted 1:5. Ten days after the third injection 20 mice in each group were bled for determination of serum antibody titres in the pooled specimens. On the same day the remaining 20 mice in each group were used in a "challenge test" employing active MEF-1 virus inoculated intracerebrally (0.03 ml.). This test was performed to provide a direct measure of immunity, the challenge dose of virus being two hundred 50% mouse lethal doses (200 LD₅₀).

(ii) *Monkeys*.—Four normal rhesus monkeys were used; two received undiluted vaccine and two the vaccine diluted 1:10. Each animal received three inoculations of 1 ml. intramuscularly, the second dose being given one week after the first, and the third dose four weeks after the second. Monkeys were bled before the immunization course and two weeks after the final injection. Sera were tested in the tissue-culture neutralization test to determine antibody titres to the three virus types.

(iii) *Man*.—Fifteen volunteers from the medical staff and students at Sheffield University received vaccine. The