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Problems in Acute Head Injuries

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"There is nothing which persevering effort and unceasing diligent care cannot overcome."—Seneca.

The writer is engaged in the preparation of a thesis centred around 1,500 acute head injury cases which have been accurately documented and personally observed during a period of two years. A small but very interesting group of patients accumulated who had sustained a "closed" cerebral injury and were admitted in a Stage 4 level of consciousness.* They lingered on for periods of varying duration at the same level of unconsciousness, developed no other gross neurological deficit and exhibited a fairly constant high level charting of respirations, temperature and pulse frequency; the blood pressure, particularly the diastolic, readings were raised. The general muscle tone was diminished and posture abolished. These patients required tracheotomy for increased secretions in the air passages. Then, as a rapid terminal event, the respiration, temperature and pulse readings raced away, the hypersecretion became virtually uncontrollable, with perhaps late decerebrate rigidity manifesting itself for a short while, and the patients died. Cerebral angiography and exploratory "burr-holes" revealed no extradural, subdural or intracerebral haematomata or cerebral lacerations, and the only significant operative findings were tight, swollen, non-pulsatile brains which transmitted neither respiratory nor arterial excursions. The autopsy findings were equally unsatisfactory, being merely a swollen brain with flattened convolutions, which cut with ease when sectioned (in contrast to the difficult, sticky slicing of a normal brain), with little, if any, tentorial hiatal herniation and with no gross macroscopic or microscopic evidence of lethal lesions; there were no haemorrhagic or ischaemic features in the grain stem. The lungs showed appearances variously described as "generalised bronchopneumonia, hyperacute pulmonary oedema, wet lungs, etc." The adrenal presented various appearances. In patients who survived for a reasonable time, the microscopic lesions usually ascribed to anoxia, viz., loss of cells from the cerebral cortex, Ammon's horn, globus pallidus, and the Purkinje cells,[1] were absent. Anoxia thus does not seem to be the primary etiological factor.

There seems to be no doubt that the initial brain dysfunction is due to mechanical upset

* LEVELS OF CONSCIOUSNESS USED IN THIS INVESTIGATION

Normal.—This is defined as the awareness of a person to his past and present external and, to some extent, internal invironments, plus calculated registration of same and positive or inhibitory responses to such environmental stimuli. "Remembering, appreciating, judging, comprehending, thinking and responding."

First Stage of Deficit.—Loss of accurate awareness, critical registration and accurate responses, with noticeable release of inhibition or restraint current in civilised communal life. The patient is capable of answering simple questions such as, "What is your name?" "Where do you live?" "What is your wife's name?" but answers incorrectly when asked such questions as, "What day is it?" or "What time do you think it is?" Such questions require insight, judgment and comprehension. These patients can swallow normally and will feed themselves on occasions.

Second Stage of Deficit.—Inhibition of awareness, registration and calculated response, characterised by light, drowsing sleep-like unconsciousness. This is penetrable with ease by minor stimuli of the crude variety and produce purposeful, reflex, evasive responses calculated to effect escape from these stimuli. Replies to the questions quoted in the first stage are answered very incompletely, if at all, and direct commands like, "Open your eyes/mouth," or "Lift up your arm/leg," are vaguely obeyed or produce only reactions like, "Go away," invective, or pulling up the bed clothes and turning away from the questioner. If food or drink is put to his mouth he will swallow easily.

Third Stage of Deficit.—A more intense form of the second stage with medium unconsciousness, penetrable only by more intense forms of crude protopathic stimuli, and likewise these initiate crude defensive reflex reactions which, however, still retain a considerable semblance of purpose. (The stimuli used were (i) kneading the lower axillae firmly with the knuckles; (ii) nipping the nipple tips strongly; (iii) squeezing the testes; and (iv) deforming the thumb and hallux joints by firm compression.) Loudly spoken orders or simple questions may produce a vague vocal or physical response. The patient will swallow if spoon-fed slowly and patiently.

Fourth Stage of Deficit.—A stage of deep unconsciousness characterised by upset of static normal tonus and thus readiness for reaction. Only the crudest stimuli, e.g., gross pain, produce responses which are not co-ordinated purposeful reactions. The swallowing function is grossly disorganised. There are features of early disorganisation of the bodily vegetative functions.

Fifth Stage of Deficit.—A stage of very deep unconsciousness with no neo-cortical, paleo-cortical or thalamic awareness, registration or response, and very marked disorganisation of the bodily vegetative functions, as shown by the pulse, respiration, temperature and blood pressure readings and the hypersecretion.

Death.—Characterised by equilibrium with the internal and external environments: no awareness, no registration and no response.

of the brain cells, particularly if the head trauma tends to cause shear strains with swirling movements of the brain within the skull. The continuance of the brain dysfunction must be due to pathological change of a micro-cellular biophysico-chemical nature which is widespread or which has widespread effects; the actual lethal effects must be in the diencephalo-mesencephalon, caudalwards from the lamina terminalis. Experimentally, the "mid-brain animal" can continue its vegetative metabolic functions without cerebral assistance, so the rapid final decline must be when the brain stem fails. The popular press in all countries always gives much publicity to comparable patients who linger on in a similar unconscious state; for example, the British boxer Jackie Tiller, of Sheffield, who was knocked out in May, 1957, and lived in a "vegetable" state until 14th April, 1958, having been in coma for 293 days. A similar state of affairs must also obtain in those cases where an acute space-occupying lesion, e.g., an extradural, subdural or intracerebral haematoma, has been removed successfully, brain compression and shift herniation corrected, and yet the patient deteriorates and dies; autopsy often reveals no gross brain stem ischaemic lesions. In this paper emphasis will be laid on the traumatic disturbances in the brain stem and its connecting tracts with other proximal and distal areas. The writer feels that, important as they are, contusions, cerebral lacerations, extradural, subdural and intracerebral haematomata, etc., are but complicating, concomitant manifestations of the forces which have also produced the lethal intrinsic microcellular damage to both the cerebral cells and the vital brain stem. It is likewise pertinent to inquire, "What actually is the killing factor in meningitis or a case of late initial recovery from cardiac arrest?"

It would seem that these microcellular biophysicochemical pathological changes must be of a cellular metabolic nature, and the fact that the above-mentioned type of head injury is the one usually helped by "hibernation regimes" (which depress the general bodily metabolism) adds further support to this premise. Therefore a proper understanding of the cerebral cellular metabolism is essential, e.g., the interrelationship of the electrolytes, the fluid exchanges, the energy requirements and the normal method of energy production, the mechanisms which increase, decrease and neutralise the cerebral, hypothalamic and distal brain stem excitabilities, the nature of the chemical mediators in the cerebral cells and the central autonomic system, the exact nature and *modus operandi* of the blood/brain, blood/cerebrospinal and the brain/cerebrospinal barrier systems, the exact roles of the various naturally occurring steroids and other hormones in all these processes, the significance of no cerebral lymphatic system—all these must be elucidated before curative therapies can be devised to reverse the above mentioned biophysicochemical pathological upsets. Once these remedies are found, the head injuries in question can be treated and other less serious brain injuries can be likewise managed with greater speed and certainty as to prognosis and possible avoidance of morbid sequelae.

It must be stressed that many head injury patients have been lost by lack of attention to the ordinary problems of management, e.g., inadequate attention to airway problems, fluid, electrolyte and nutritional requirements; in brief, they have not died because of the cerebral injury *per se*, but of gross neglect because they were unconscious and thus unable to indicate their requirements. It is therefore considered that brief discussion on these important facets of management is not out of place in the consideration of the total problem.

The whole matter bristles with great difficulty. This paper aims at presenting a considerable amount of bedside clinical observations and therapies, plus a review and "sorting out" of modern information on cerebral metabolic processes. In order to maintain some degree of clarity the various aspects will be considered under distinct headings and then an attempt will be made to correlate the findings and suggestions into definite practical treatment.

FORCES INVOLVED IN HEAD INJURIES

Under a sub-title of "Force and the Skull" in his Bradshaw Lecture,[2] H. S. Souttar considered the ability of the skull and its contents to resist the effects of an injury. "If a man is struck on the head by a stone weighing 1 lb. and falling the distance of nine feet, he would probably have a degree of concussion, although his skull may not be fractured. Let us consider the forces involved. The stone falling nine feet reaches a velocity of 24 feet per second and, as it weighs 1 lb., it has acquired 288 foot-second units of energy. If it deforms the skull a quarter of an inch, which is about the limit, it means that the resisting force must destroy this amount of energy in 1/48 of a foot, and the average force must therefore be 48 x 288 units of force or 432 lb. weight. If this were distributed over an area of the skull of 2½ inches

diameter, it would mean a local pressure of 86 lb. per square inch."

The skull is, for all practical purposes, filled by an incompressible fluid content of various specific gravities and which, for such sudden large forces, has little escape. Any deformation will be resisted by a rise in the intracranial pressure. Although the pressure increase lasts but a fraction of a second, it must have a deleterious effect on the nerve cells themselves and must empty, and possibly damage, the cerebral capillaries, with the clinical results of complete and instantaneous paralysis. Souttar's theoretical example gives us some idea of the forces involved and the consequences.

The classical studies of Denny-Brown and Russell on concussion are well known. They defined "concussion" as a direct traumatic paralysis of cerebral function without vascular lesion, the paralysis persisting for a varying period according to the type and severity of the causal trauma. They observed that the concussion was more easily produced if the head was free to move in the direction of the impact, and they deduced that the two mechanisms which may produce it were acceleration and compression. They stressed the importance of acceleration by demonstration that acceleration from rest to 28.4 feet per second is necessary before detectable effects on the brain stem are manifest. This is obliquely confirmed by the fact that the most effective knock-out blow in boxing is the chin uppercut which travels only a few inches, but at immense acceleration. An important etiological force, in the writer's opinion, is the rotational acceleration as distinguished from the linear acceleration of the semi-fluid brain within the skull. The brain tissues are of different specific gravities and the traumatic results of the rotational acceleration are most marked at the interfaces of the brain layers of different specific gravities. Another important observation of the above-mentioned investigators was that when the intensity of the trauma was increased over the threshold which produces concussion, the effect is to prolong the cerebral paralysis, although still no lesion is seen. The rate of recovery of the neuronal injury is thus proportional to the degree of trauma; it is conceivable that the amount of neuronal injury that can be produced is so great as to become irreversible.

They also produced varying degrees of concussion in decerebrate animals and others under artificial respiration, thus showing that this condition can develop independently of the telencephalon and respiratory failure. In contradistinction to Trotter's cerebral anaemia theory, these observers reported that immediate paralysis of concussion was not associated with a decreased blood flow through the brain. Throughout the investigation emphasis seems to be placed on the disturbances caused in the brain stem by the trauma. Thus these observations and the absence of damage due to anoxia (see *supra*) cast considerable doubt on the validity of the usual indictment of cerebral ischaemia and/or cerebral anoxia as the cause of death in the group of head injuries under consideration.

In the writer's opinion the basic problem is that of a large, heavy, soft, incompressible mass of supratentorial cerebrum anchored by a more compact firm brain stem, which passes through the narrow tentorial hiatus. Comparatively speaking, the cerebrum is freer to move by gliding or shearing than the relatively fixed brain stem (fixed by the optic nerves, pituitary in its fossa, the emerging nerves bundles and, to a lesser extent, by its blood vessels). Even if the problems of downward displacement of the brain stem, coup and contracoup blows on the basisphenoid and the sharp edge of the tentorium and the strains on the blood vessels are ignored, there is still a considerable shear jerk at the upper brain stem region (the junction of the fixed and movable parts)—enough to cause local traumatic inhibitions of considerable degree. Therefore, when the effects of acceleration, deceleration, compression and shear stresses are considered, it would appear miraculous if the hypothalamus, anchored as it is, was to escape from the effects of severe cranial trauma; and if concussive paralysis developed in this vital area and was prolonged, then the results could be disastrous. Le Gros Clarke [3] established that effector mechanisms in this area control pulse, respiration, temperature, blood pressure, etc., and in general this portion of the brain controls the vegetative functions of the body. This is in direct contrast to the general functions of the neighbouring thalamus (especially the neothalamus), which is concerned with definite stimuli originating in the external environment. He also showed that there were direct neural pathways between the hypothalamus and a portion of the prefrontal cortex, and suggested that this cortex was a projection area of the lower centres. Experimental and accidental operative traumata to the hypothalamus have been followed by upsets in the pulse, respiration, blood pressure, together with hyperthermia and hypersecretion (abnor-

malities usually attributed to brain stem lesions), coupled with various degrees of unconsciousness as well as memory defects, apathy, loss of critical judgment and appreciation, and behaviour restraint (abnormalities usually attributed to frontal lobe lesions).

Two final observations from the writer's own studies concerning the effects of trauma on the brain are:—

(i) The relatively mild disturbances of cortical and vegetative functions accompanying the shattered skull ("reminiscent of the top of the breakfast boiled egg"). Several of these cases in the major series suffered from ordinary concussion only —a feature quite out of proportion to the severity of the skull fractures. On the other hand, the majority of the cases which form the subject of this paper had no skull fractures on X-ray examination or at autopsy.

(ii) Several cases in the major series sustained compound fractures and proven cerebral lacerations, but were never at any time unconscious.

In brief, the basis for subsequent expansion of this paper revolves around the following premises that the initial results of the head trauma are—

(i) traumatic discharge and then inhibition of the cerebral cells;

(ii) traumatic discharge and then inhibition of the cells of the hypothalamus and the brain stem tegmentum tissue.

These effects could almost be called "central neuropraxia," thus bringing them into line with the possible similar results of trauma on the peripheral nerves.

If the above effects of trauma are extreme and prolonged, then death will soon occur. If they are not so severe or prolonged, then the sympathetic central vegetative mechanisms are called into action as a protective and reparative measure. After a while the parasympathetic mechanisms emerge and become effective and a sympathetic/parasympathetic balance of action is attained and normality is restored. In essence, the activities of the sympathetic system are directed towards the mobilisation of all the bodily resources to deal with emergencies, whereas the activities of the parasympathetic system aim at conservation and restoration of the bodily resources to a normal resting phase. A well-trained boxer can be reduced to a Stage 4 unconscious state, recover in less than 10 seconds and thus beat the count, and then go on to win the fight by superior boxing. This extreme example illustrates that it is quite impossible to predict the recovery rate, which may involve a facilitation process.

However, if the return of the parasympathetic activity is delayed, then the sympathetic unbalanced action continues chronically and unabated; ultimately the invoked mechanisms collapse, with resultant delayed death of the patient. In the writer's opinion this is the group of head injury patients with which this paper deals, and the line of therapeutics which he is exploring is to damp down the sympathetic action and to enhance the parasympathetic recovery. The not infrequent rapid recovery of young children who sustain the type of head injury under discussion may be related to the probable slight preponderance of the parasympathetic system in these growing youngsters.

GROSS GENERAL NUTRITION

The following matters are of great importance and interest in the management of any unconscious head injury patient. The writer has always felt that much morbidity and even mortality occurring amongst these patients who have survived the initial effects of the brain trauma is due to gross malnutrition and avoidable fluid and electrolyte abnormalities.

The unconscious state due to head injuries is, at least primarily, a relatively "pure" type, metabolically speaking, in contradistinction to the gross primary metabolic upsets of coma in diabetic, uraemic, hepatic disease and anaesthetia. It was therefore felt that, provided adequate attention was paid to the gross metabolism needs, it may be possible to explore the finer upsets in brain metabolism concerned in the continuance of the unconscious state. Again, the understanding of stress and the biological responses to it are much easier when the patient is purely unconscious, because the responses are automatic and without regard to conscious or emotional stimuli. These automatic responses are thought to be mediated chiefly through the hypothalamus and associated lower centres and tracts. Although Selye and others have shown that the ability to survive stress, and responses thereto, requires an intact functioning pituitary-adrenal system, the present evidence suggests that the chief regulating centre of neural and hormonal responses is the hypothalamus.

Therefore the major investigation was begun with the premises that—

(i) "adequate nutrition is a fundamental requirement for life and health; even short periods of

starvation can only be detrimental; in every case where the patient cannot feed himself there must be a supply of all the nutritional requirements until he is able to feed himself";

(ii) "supply of these nutritional requirements and metabolic regulation thereof by natural physiological ingress are vastly superior to intravenous therapy, and the former alimentation should be used whenever possible; in these head cases the intestinal system usually works normally. When the patient cannot swallow normally, a soft rubber or polythene tube was passed into the stomach and nourishing fluids were administered by this means. Accurate input/output charts were kept during the period of this therapy."

Any clinician who has looked after these unconscious head injuries will agree with the writer's opinion that a combination of negative nitrogen and calorie balance, dehydration and unconsciousness is a fatal combination.

Experimental metabolic work has shown that if a patient is to be maintained in positive nitrogen balance he must receive a high calorie intake with a basal amount of first class amino-acids. The basic minimum calorie requirements of the average adult are 1,500 calories per 24 hours, and an active adult needs 2,500 calories to remain well in calorific balance. If less calories are supplied, then endogenous and enogenous protein is utilised and soon the patient is in negative nitrogen as well as negative calorie balance. On the average, a normal adult consumes 50 per cent. of his calories from carbohydrate sources, 15 to 25 per cent. from proteins and 25 to 35 per cent. from fats. In acutely sick patients it would appear clinically that fat is burnt with difficulty and that endogenous protein is a more facile source of calories.

Despite the stated preference for alimentation feeding, the writer has found by experience that patients with meningitis, shock from blood loss or associated major injuries where the renal function may be decreased by the resultant hypotension, deeply unconscious patients with some hypopotassaemic abdominal distension and subnormal urinary output, or similar neglected patients, are easier to restore to balance (fluid, electrolyte, calorie and nitrogen) by brief intensive intravenous fluid therapy than by alimentation. However, as soon as the acute problems have been remedied, the latter feeding method was instituted.

Despite the various commercial products which are available, the writer has always preferred to use natural foods for these patients. These are economic, and milk, meat, potatoes, fruits and vegetables contain enough proteins, calories, minerals, vitamins and other essential nutrients. To get these substances in a physical form suitable to pass down a narrow-bore tube can be done by either a "Mix-Master" mechanical blender and juice extractor or by using the ready-made strained baby foods diluted with milk or water. For example, one tin each of a well-known product meat and vegetable baby foods plus two large eggs and a pint of top grade milk will supply almost 60 grams of first class protein and 900 calories in a physical state which can be squirted down a naso-gastric tube without overdistension of the stomach. Glucose, commercial milk, meat extract fluids can also be used to supply fluid, electrolytes, protein and calories.

Because the vast majority of the patients seemed to suffer from relative degrees of deficiency of vitamin C and the B complex, as shown by subclinical stigmata of scurvy and hyporiboflavinosis, big doses of these vitamins were given intramuscularly each day while the patients were in the acute stage of their illness. The importance of this therapy will be stressed later.

Oblique but interesting support for this concentration on gross metabolism in head injuries is supplied by the finding that schizophrenic and manicdepressive patients often exhibit physical signs that can be interpreted as evidence of metabolic general disorders; in particular, their body weight may be subject to marked fluctuations. In the past these weight losses were attributed to inadequate food intake and overactivity, and weight gains to overeating and sedentary habits; thus the weight changes were considered to be secondary to the patient's mental state at the time of observation. Crammer [4] has, however, been able to show that considerable weight changes may occur before the change in the mental symptoms. He observed cyclic changes of as much as 9 lb. in 24 hours weight loss in three patients with periodic catatonic schizophrenia. This sudden loss in weight usually coincided with an acute flare-up of the catatonic symptoms. In two of the three patients both the acute mental episodes and the preceding drop in weight were abolished by chlorpromazine (see later discussion on this drug). Crammer is of the opinion that the weight changes observed were the results of losses in the body water and salt in the urine, and they were not a consequence of the mental symptoms, but were physical signs of the pathological process underlying the mental illness.

The possible role of the hypothalamus-pituitary-adrenal cortex complex in these upsets in

cerebral metabolism and function assumes great importance. The writer feels that dysfunction of the hypothalamus is intimately concerned in the type of head injury under review, and close attention must be paid to gross general metabolism so that the finer and obscure metabolic upsets can be elucidated.

Respiratory Problems in Head Injuries

S. S. Kety and C. F. Schmidt [5] have shown that in a man lying at rest the brain is responsible for the utilisation of about one-quarter of the total oxygen used by the body and that oxygen consumption also varies with the level of the cerebral activity. In contrast to most of the other tissues of the body, the brain seems to oxidise glucose almost exclusively; this is shown by the respiratory quotient of the living human brain being virtually 1.0 from estimations in samples of carotid and jugular blood.

Cerebral grey matter has a higher rate of oxygen uptake in the presence of glucose than has the white matter and peripheral nerves have a still lower rate. This high rate of oxygen consumption of the grey matter is not just by the cell bodies, because E. G. Holmes [6] found that the trigeminal ganglion, a structure containing cell bodies but no dendrones or synapses, has a relatively low respiratory rate.

Following the techniques of Kety and Schmidt, M. L. McCall [7] investigated cerebral blood flow, cerebral metabolic rate in terms of oxygen, cerebral vascular resistance, respiratory quotient and nutritive index of the brain in normal young men, normal pregnant women, women with hypertensive toxaemia and others with eclampsia. The coma and pathological appearances of the brain in eclampsia are often rather similar to those of the head injuries under discussion, so it is quite interesting to examine the results of this investigation. In brief, in eclamptics the oxygen consumption of the brain was depressed. However, the amount of oxygen carried to the brain in these cases was virtually unaltered, and this would point to the likelihood that there is some disturbance in the brain cells themselves, rendering them less capable of using the available oxygen. Although McCall's findings obviously cannot be applied directly to the head injury cases, because of the different etiologies of the two conditions and the gross extracerebral pathology in eclampsia as opposed to the relative lack of this in the head injuries, the results are significant. His methods and formulae should be done in a group of the head injuries by an investigator with adequate laboratory facilities; the writer predicts that comparable findings will be forthcoming.

In view of the enormous oxygen requirements of the brain, there can be no doubt that the maintenance of a perfectly clear airway is a vital necessity in patients who are unconscious because of head injuries. In practice, anoxia may be due to blood loss, a sequence of severe scalp haemorrhage, shock from severe associated injuries or gross thoracic cage trauma, but the commonest cause by far is respiratory obstruction by retained secretions. For many years clinicians did not appreciate this hazard. Latterly, lateral positioning of the patient, two-hourly change of position, intermittent pharyngeal suction, toilet and oxygen administration have been used to combat this mechanical respiratory complication; only in recent years has the very great efficiency of early tracheotomy been realised.

The reflex efforts to overcome the respiratory blockage lead to raised venous and arterial pressures and the muscular activity uses up the vital oxygen and predisposes to toxic carbon dioxide retention. Also the laboured breathing causes increased intrathoracic tension, and as the cerebral veins have no valves, this increased venous pressure is directly transmitted to inside the skull. Therefore there will be increased intracranial pressure, generalised cerebral vasodilatation, anoxia and carbon dioxide retention —all of which will severely embarrass cerebral cell metabolism.

Presumably the function of the normal secretions of the respiratory passages is to moisten the incoming air, dilute inhaled irritants and to trap particulate matter. Normally, the reflex flow thereof is stimulated by local contact stimuli and the flow is produced by central autonomic impulses; salivation behaves in a roughly similar way. In the deeply unconscious patient the integrity of the reflex mechanism is probably disturbed, and disordered excessive autonomic motor activity may result in hypersecretion accompanied by loss of the protective coughing mechanism of expulsion. In the later stages inadequate right heart filling, due to the racing cardiac rate, may contribute considerably to the obstruction to aeration by gross pulmonary oedema.

Tracheotomy (performed immediately in presence of respiratory distress or in any severely comatose head injury of more than 24 hours' duration) can assist greatly in the maintenance of a clear airway; ancillary suction is

also more effective through the artificial air passage. However, the use of the time-honoured tracheotomy tubes has many disadvantages; the constant presence of the tube, which invariably stimulates by irritation the posterior mucosa, leads to further secretion in the whole bronchial tree. The deglutition mechanism is hindered and, despite the heroic efforts of staff by cleaning, suction and tube changing, it is virtually impossible to cope with the hypersecretion in these patients. For some 15 years now the writer has abandoned the use of the classical tracheotomy tube and instead he creates a tracheal fistula of adequate size by resecting a disc from the anterior wall of the trachea and sutures the skin edge down to the margin of the tracheal hole, thus excluding the neck tissue planes from possible interstitial emphysema and leaving a wide open fistulous communication. This is lightly covered by a square of one thickness of surgical gauze. These holes have much fewer deglutition problems and oesophageal reflux, are easily cleaned and sucked, work extremely well in small children and always close without complications.

CELLULAR PHYSIOLOGY

In order to emphasise the peculiar arrangements in the cerebral cells, a brief survey of the conditions obtaining in the non-cerebral cells is worth while. Here the constituents of the blood plasma are in fluid continuity through the capillary wall with the extracellular fluid medium, and this latter medium is also in similar continuity through the cell membrane with the protoplasm of the cell. Through this continuous medium metabolic exchanges between the blood plasma and the cell occur, subject to specific permeable processes, specific gradients, enzymes and hormones. The extracellular spaces have volume and dimension and ultimately drain into the local lymphatics, and a proportion of the plasma/cell transudate and contained metabolites are thus transported back into the blood stream. Ingredients of molecular weight of less than 40,000 pass easily through the capillary walls, and albumen and the smaller globulins of somewhat higher molecular weights can also so pass; possibly the chief function of the lymphatics is to carry away these larger ingredients by an easier path to the blood stream. This fluid turnover from plasma to extracellular spaces to the blood plasma again is a dynamic circulation.

One response to local trauma is an increase in the capillary permeability, and this results in a rich plasma exudate into the extracellular space. Thus the extracellular fluid contains nearly as much albumen and smaller globulins as the plasma remaining in the capillary, and the actual fluid volume is also increased. At the same time, there is an increase in the sodium content of the injured cells, wherefrom, at the same time, potassium is released by the injury. To restore the normal *status quo*, and particularly to facilitate the removal of the albumen and globulins, the dynamic lymphatic flow is speeded up; but local space expansion occurs because the rate of loss of plasma fluid from the capillaries exceeds its rate of return both locally to the capillaries and *via* the lymphatic circulation. The local rest in response to pain reflexes probably retards the dynamics of the lymphatic circulation.

An obvious conclusion from the above is that the extracellular medium/lymphatic/vascular circular system plays an important part in the restoration of the normal *status quo* of electrolytes and water of the extracellular space-cell complex after metabolic and injury disturbances.

CEREBRAL CELLULAR PHYSIOLOGY

A brief discussion on the blood/brain barrier is necessary, because this definitely selective barrier is intimately integrated with cerebral cell functions. That such a barrier exists is shown by the following known facts:—

(a) In various types of jaundice in the adult, most tissues are deeply stained by the bile pigments, but the cerebral tissues and cerebrospinal fluid are not. In icterus neonatorum more or less severe central nervous system symptomatology is common and involvement of this tissue has a bad influence on the prognosis of the condition. At autopsy there is often severe bile staining of the nervous tissue, particularly the basal nuclei.

(b) Evidence is slowly accumulating that serotonin has a definite function in maintaining normal cerebral processes, and interference with its activity in the brain is followed by neurological dysfunction and mental disorders. Serotonin is thought to be very active in producing central synaptic inhibition. The natural precursor of serotonin is 5-hydroxytrytophane, which can easily pass through the blood/brain barrier and may increase the serotonin content of the cerebral tissues. Serotonin is found naturally in many other tissues of the body, particularly the intestines. In the brain it is found everywhere, but the highest concentrations are in the hypothalamus and the least in the cerebrum and cerebellum. The blood/brain barrier has a remarkable power of resisting the entrance of systemic serotonin into the brain, as shown by the absence of gross neurological upsets, the steady maintenance of normal neural content and its continued absence in the cerebrospinal fluid, when the blood content is raised by either injections of the substance or by excessive

amounts derived from the malignant carcinoid neoplasms of the intestines.

The anatomical barriers between the blood plasma and the intracellular fluid are as follows:

(i) The single layer of capillary endothelium cells.

(ii) The sucker feet of the neighbouring astrocytes.

(iii) A ground substance of a mucopolysaccharide composition.

(iv) The neural cell membrane.

(i) If the vascular endothelium is the seat of the barrier action, this thus infers that this endothelium has specialised properties not possessed by capillary endothelium elsewhere in the body; this is very unlikely.

(ii) Neural axons do not have these sucker feet associated with them, and yet these axons are part of the mother cell and presumably function through a similar neural mechanism. So it does not seem that the barrier is here.

(iii) The mucopolysaccharide ground substance would appear to be the only local stratum capable of exercising this important barrier function; possibly systemic hormones are utilised by it to exert this specialised control. It is a relatively late development in the embryonic brain.

(iv) The neural cell membrane is considered to have a vital role to play in the actual cell function, which would be impeded if the membrane had to cope with barrier work. A short resume of the theory of neural cell function will show that this requires a stable pericellular medium insulated from extraneous instabilities.

Theory.—There is thought to be a steady potential difference between the interior and exterior of each cell—the so-called resting membrane potential. Cell function is the consequence of the selective permeability characteristics of the cell membrane and the concentrations of ions at the intracellular and extracellular surfaces of this membrane. Excitation processes of the brain cells appear to be associated with such transmembrane ionic shifts. Increased sodium ion concentration within the cell or relatively decreased extracellular sodium ion concentration accompanies increased brain excitability; decreased intracellular sodium concentration or relatively increased sodium ion concentration outside the cell accompanies decreased brain excitability.

There is considerable evidence that potassium ions are rather less important than sodium ions in these vital biological processes.

According to the classical theory of nervous conduction, the passage of the nerve impulse involves a depolarisation of the cell membrane. As is the case in other body cells, the potassium content of the brain cell is 10 or 20 times higher than that of the extracellular medium, the blood or the cerebrospinal fluid, while the sodium and chloride concentrations are much higher in the extracellular medium than within the cells. At rest, therefore, there is a considerable gradient of these ions across the cell membrane. Since studies with isotopes have shown that these ions can easily penetrate the cell membrane, it would appear that some "force" (energy or hormonal complex) is required to hold these resting gradients. The passage of the excitation is accompanied by a passage of sodium ions into the cell and a *pari passu* passage of the potassium ions out of the cell; this could follow the ionic gradients after neutralisation of the gradient holding force and thus require no gross energy output for its speedy occurrence.

The recovery processes are associated with an extrusion of the sodium ions and the re-entry of the potassium ions into the cell. The restoration to normal resting potential state after excitability is against the biochemical ionic gradient and requires energy; glucose is the principal source of energy in cerebral metabolism. Glutamic and aspartic acids appear to be intimately involved in the transfer of both sodium and potassium ions across the cell membrane; these amino acids turn into their corresponding amines, viz., glutamine and asparamine, and this amination requires oxidation of glucose. The brain has very small stores of glucose and is thus very dependent on constant regular supplies from blood stream glucose for recovery in the post excitement phase; likewise, normal supplies of blood oxygen and efficient removal of local carbon dioxide are essential, and any general factor which interferes with the normal availability of these essential chemicals will seriously impede the normal recovery of the cerebral cells.

It is conceivable that when the neural cell is stimulated by trauma an excitatory phase occurs with its customary ionic shifts. If the cellular and extracellular media are relatively unchanged by the trauma, then the recovery processes will occur and the cell will return to the normal resting phase. However, if the trauma is severe enough to alter the permeability of the capillary endothelium with an unrestrained increased outflow of electrolytes, water and protein substances, etc., into the damaged pericellular ground substance, this disturbance makes return to the normal resting phase impossible and so further functioning of the cell cannot occur. The cerebral tissue has no true interstitial spaces or lymphatics to drain away the abnormal substances, and the presence of these latter must be a continued source of embarrassment to cellular function. The extravasations from the injured capillaries into the pericellular ground substance must contribute largely to what is loosely described as cerebral oedema. This latter can possibly embarrass the

cerebral circulation and thus the oxygen, carbon dioxide and glucose exchanges locally.

The whole matter of restoration of the cell to a normal resting state in normal and abnormal conditions has not yet been totally revealed. The writer feels that the hypothalamus-endocrine system is intimately involved through specific actions of blood-born hormones or similar substances. An interesting point which requires elucidation is whether cerebral cells, held in abnormal discharge phase, atrophy or not. If the hypothalamus cells are traumatically stimulated and there is non-return to normal resting phase, then the patient will die; conversely, minimal trauma will be quickly followed by return to normality. Between these two extremes are many gradations, the effects of which depending on local ability to function and reflex influences from peripheral endocrines. At first there may be a relative increased activity of the central sympathetic section of the hypothalamus with the purpose of re-establishing the normal cerebral and hypothalamic states. Primarily these will be beneficial for the survival of the animal, but continued central sympathetic hyperactivity or, conversely, unbalanced relative depression of the central parasympathetic portion of the hypothalamus (a system whose general activities are chiefly aimed at restoring bodily tissues to their resting phases) can only result finally in failure of the whole system and death of the animal. The beneficial effects of Chlorpromazine and Serpasil (*vide infra*) in these cases may be explained by their ability to depress the central sympathetic and/or elevate the central parasympathetic centres and thus restore the whole hypothalamus to a balanced equilibrium. Apart from the effects of this on the vegetative system, attempts must be made to elucidate the roles of the adrenal hormones, the thyroid hormone, etc., on the normal and abnormal physiology of the cerebral cells. The pathways by which information concerning the *status quo* of the cerebral cells is conveyed to the hypothalamus are unknown, but these must be elucidated in any formal investigations of the foregoing suggestions. The remainder of this paper aims at exploration of these hypotheses.

RELATIONSHIP OF ADRENAL CORTEX HORMONES TO BRAIN EXCITABILITY

D. M. Woodbury[8] emphasises the marked regulatory influence of the adrenocortical steroids on brain excitability and suggests that there is a definite relationship between this influence and the steroid influence on electrolyte metabolism. In this investigation it was shown that deoxycorticosterone (which is not a naturally occurring corticosteroid) causes—

(i) a decrease in intracellular sodium ions;
(ii) an increase in ratio of extra- to intracellular sodium ions;
(iii) a decrease in brain excitability;
(iv) increase in concentrations of glutamic and aspartic acids in the brain and a corresponding decrease in concentration of glutamine and asparagine;
(v) no effects on cerebral blood sugar levels.

Aldosterone, a normally occurring electrolyte regulating steroid of the adrenal cortex, acts very similarly to deoxycorticosterone, but less strongly. Dilantin acts like these steroids.

In contrast, 17-hydroxycorticosterone acetate causes—

(i) an increase in intracellular sodium ions;
(ii) a decrease in ratio of extra- to intracellular sodium ions;
(iii) an increase in brain excitability;
(iv) a decrease in concentrations of glutamic and aspartic acids and a corresponding increase of glutamine and asparagine.

THE ROLE OF THE THYROID GLAND IN CEREBRAL METABOLISM

This does not seem to be completely established, but the following points have been elucidated:—

(i) Thyroxine influences cerebral metabolism partly by direct action and partly by indirect action *via* the adrenal glands.
(ii) Thyroxine influences the electrolyte distribution, particularly sodium, in the brain.
(iii) Its absence causes a considerable decrease in cerebral blood flow and a similar decrease in cerebral oxygen and glucose consumption.
(iv) Conversely, in hyperthyroidism there is hyperacute mental activity and labile emotional status, occasionally bordering on psychosis.
(v) There is marked improvement in the mental lethargy of myxoedema from the fourth day onwards after thyroid therapy.
(vi) Ordinary psychotics often show a slight hypothyroidism and the mental side of the symptomatology improved when given thyroid only.

There is enough in these data to emphasise the important role of the thyroid gland in cerebral metabolism.

AUTONOMIC REPRESENTATION IN THE BRAIN

The nervous tissue concerned with the autonomic functions develops from the primitive grey matter which clothes the cephalad end of the primitive neural tube (compare the position of visceral afferent and efferent peripheral cells) and are represented in the formatio reticularis of the brain stem tegmentum and the highly

specialised hypothalamus in the developed brain. The formatio reticularis, which probably retained several of its primitive functions, has a different specific gravity from the more compact fibre tracts which are disposed around it and thus may be traumatised much more easily.

If the hypothalamus exerts an important regulatory control on cerebral as well as general bodily metabolic changes, then it must have some sensitive receptor-appreciation mechanism to pick up such changes and an afferent conducting pathway to transmit such information to it. The only other alternative is that the hypothalamus itself contains such an appreciation-receptor mechanism. The writer suggests (without any really concrete evidence) that a principal function of the tegmental formatio reticularis is to appreciate metabolic upsets, particularly those in the brain, and to relay such information to the hypothalamus, and this structure then sets in motion general metabolic activities to correct the upsets. The information may be carried to the reticular tissue by both the blood stream and by the innumerable nerve fibres which end in this tissue. In contrast, the area of cortical projection of the hypothalamus itself seems to be comparatively limited. The scanty evidence which may support the suggestion is the frequent finding of a dilated Iter in the brain stems of "punch drunk" boxers, the dilatation being possibly due to atrophic shrinkage of the surrounding reticular tissue and the traumatic encephalopathy due to impairment of the appreciator receptor mechanism. E. R. Bickerstaff,[9] under the title of *Brain Stem Encephalitis*, reported a series of eight cases; these were characterised by initial drowsiness and then gross brain stem neurological defects of such severity that survival for even a few days seemed impossible. All except one patient, however, did survive, with virtually no residual deficits. The brain stem of the fatal case showed widespread swelling and ballooning of the myelin sheaths of the less compact fibre tracts, and a photograph of the ventral tegmental tissue at the level of the emerging oculomotor fibres is shown.

The autonomic centres in the tegmentum of the medulla oblongata are those mainly responsible for control of respiration and circulation. Phylogenetically, this is in accord with the intimate relationship of this part of the brain with the branchial apparatus. These not only maintain the blood pressure and chemical composition within normal limits, but also make possible several complicated multisegmental reflexes, such as the carotid sinus and aortic arch reflexes, coughing, sneezing, vomiting and swallowing. However, the medulla does not play any important part in the central regulation processes and is controlled by higher centres in the brain stem tegmentum.

Information concerning the functions of the formatio reticularis in the mid brain are not at all clearly defined. Nevertheless, experimental "mid brain" animal and other investigations demonstrate that this tissue is functionally more highly developed than that of the distal brain stem, and that, if dissociated from the controlling influences of the more proximal centres, this area can carry on a considerable amount of the bodily vegetative functions on its own accord. Important stations for bladder control, sleep and waking states, buccal, respiratory and alimentary tract secretion have been described.

The most important region of higher autonomic regulation is in the diencephalon—principally the hypothalamus. Anatomically, the hypothalamus embraces the optic chiasma, anterior perforated substance, the hypophysis cerebri, infundibulum, tuber cinereum, corpora mammillaria, the posterior perforated substance, the subthalamic tegmental region and the anterior part of the lateral wall of the third ventricle below and in front of the thalamus. Neurologically, however, the hypothalamus is regarded as the structures in the anterior part of the floor of the third ventricle, excluding the chiasma and the hypophysis, and the lateral wall of the ventricle below and in front of the hypothalamic sulcus. The subthalamic tegmental region is the upward continuation of the distal brain stem tegmentum and contains very many afferent and efferent fibres between the formatio reticularis and the hypothalamus. The anterior and medial thalamic nuclei (paleothalamus) have connections with the hypothalamus and project to the frontal cortex and posterior orbital and cinguli gyri.

Recently, evidence has accumulated to suggest that the anterior part of the "neurological" hypothalamus has central parasympathetic functions and the posterior part has sympathetic functions. Countless experiments on this region and stimulation by irritation, trauma and local disease have produced unbalanced upsets in the bodily vegetative functions as responses.

The writer suggests that the hypothalamus and the tegmental structures suffer considerable disturbance of function when a serious head injury occurs, particularly if caused by rotational

acceleration forces. The resultant "central neuropraxia" evokes a sympathetic response which, though beneficial initially (and if brought back into balance by resurgence of the parasympathetic action, it will restore the patient to normal), nevertheless will lead to ultimate death of the patient if it is prolonged and uncurbed by the parasympathetic restraint. For these reasons the writer considers that continued increased systolic, pulse pressure, diastolic and respiratory frequency readings in an unconscious head injury patient are not signs of a vigorous cardiovascular respiratory system fighting to overcome excessive resistance in an overfilled skull box, but are signs of unbalanced and uncurbed sympathetic activity, and these will be inimical if unchecked. The salivary and respiratory hypersecretion falls into a similar category.

Accordingly, if the exact chemical transmitters in the central autonomic system and their natural and synthetic antagonists can be found, then it should be a simple problem to depress the sympathetic activity, enhance the parasympathetic activity and restore a balanced relationship in this vital part of the brain. It is felt that it is better to try to restore the normal *status quo* in the central autonomic system than to try to administer the peripherally released hormones in the hope of striking the correct combination which will restore cerebral and autonomic normality. Before the writer had fully grasped the significance of the complex disturbances occurring in these patients, he administered 25 I.U. of A.C.T.H. to two such brain injuries who were in the uncontrollable penultimate stages. He was considering the possibility that exhaustion of the hypothalamus-hypophysis was the cause of the deterioration and hoped that the A.C.T.H. would bolster up this central system. All that he did was to accelerate the deterioration, and both patients died within two hours of the administration of the drug. This chastening experience gave rise to the theory which is propounded above.

THE NEURO-HUMERAL AGENTS IN BRAIN ACTIVITY

According to the generally accepted theories, an important controlling hormone in central parasympathetic activity is acetylcholine, and nor-adrenaline is of similar importance in the central sympathetic system. Another agent, serotonin, is present and is a known very potent inhibitor of neuronal function. The complete equation of cerebral function is a balance between excitation and inhibition of neural impulses activated by these or similar neurohormones.

The hypothalamus controls the metabolic and visceral functions, temperature, circulation, respiration, sleeping and waking states, secretion of pituitary hormones and thus distal secretions from adrenals, thyroid, parathyroid, pancreas and gonads. Control by the reticular system, stimulated by metabolic, visceral and emotional impulses, could be responsible to a large degree for the reverberatory activity between cortex and diencephalon.

The important part played by serotonin in cerebral activities may be gleaned from the following facts:—

(i) Serotonin is present in the whole of the brain; the biggest concentration is in the hypothalamus and only small quantities in cerebrum.

(ii) The blood/brain barrier is intensely selective in keeping peripheral (normally produced and injected) serotonin out of the brain, which could suggest that minute quantities may have a profound action on cerebral cell function.

(iii) An enzyme, carboxylase, which can form serotonin from its precursor, 5-hydroxy-tryptophane, is found in quantity in the brain. Pyridoxine, which is involved in the enzymic synthesis of serotonin, when absent from the diet, may lead to features of parasympathetic overactivity and peculiar chronic epileptic disorders in children.

(iv) An enzyme, monamine oxidase, which specifically inactivates serotonin, is present in quantity in the hypothalamus. Inhibition of this enzyme by iproniazid is followed by parasympathetic overactivity. A considerable quantity of clinical experimental information concerning serotonin is available, but the writer finds the conflicting conclusions rather confusing. For example, Wooley and Shaw [10] suggest that schizophrenic-like states may be the result of cerebral serotonin deficiency, and Marrazzi and Hart [11] suggest that similar cerebral upsets may be due to exactly the reverse, i.e., excess of this substance. However, it would seem that a moderate increase of serotonin may cause an upset in the normal cholinergic control of the hypothalamic mechanisms concerned in essential vegetative functions. Whatever the final answer is in these problems, it is obvious at the present stage of knowledge that the restoration of parasympathetic/sympathetic central balance cannot be effected by therapies involving serotonin.

Apart from the problems concerning the functions of serotonin in the hypothalamus, there seems to be no doubt that this substance probably plays an important part in the functional and metabolic processes in the cortical cells. Its action may be at the neuronal cell surface (? it is the releasing agent of the resting cell membrane resting electrolyte balance), or it may act in some enzyme set up inside the cell. The alkaloid, serpasil, is followed by a rapid decrease in serotonin content of the brain, which

continues for a long time. The various clinical effects, decrease of blood pressure and other "parasympathetic" characteristic actions of this and associated rauwolfia alkaloids are well known. The connecting link between serotonin and serpasil may be the fact that both contain the indole nucleus, and the latter may, by blocking substitution, prevent the normal action of serotonin.

The writer has no experience of the therapeutic use of serpasil in head injuries, but a trial series may be justified.

CHLORPROMAZINE

The writer has had considerable experience of the value of this drug in the management of over 1,200 acute head injury patients; he used Largactil brand of chlorpromazine hydrochloride (May & Baker). The remaining 300 patients who did not receive the drug were used in a rough clinical trial for comparison of results.

A. Goldblat [12] described the action of chlorpromazine as "a controlled inhibition of the autonomic nervous system." The writer's bedside unscientific impressions are that chlorpromazine possibly upsets nor-adrenaline action in the central sympathetic system and thus allows comparative central parasympathetic preponderance.

Considerable information concerning this valuable drug has accumulated since its inception, and the following statements are relevant to the theme of paper:—

(1) Dasgupta *et al.*[13] showed that chlorpromazine has a blocking action on the interneurones of the spinal cord and brain stem reticular formation. It may depress the vomiting centres in these regions.

(2) Hiebel *et al.*[14] likewise described, in an extensive investigation, the depressing action of chlorpromazine on the spontaneous activity of the formatio reticularis, and it reduces sensitivity of this tissue to sensory stimuli, including circulating adrenaline.

(3) Anton-Stephens [15] described the "somnolence" produced by chlorpromazine as similar to normal sleep, but quite different from the effect of sedative drugs, the chief characteristic being the ease of rousing the patient without clouding of consciousness.

The writer confirms this advantageous "tranquillising" action and used the drug on this account. Valuable clinical evidence of increasing deficits in level of consciousness were not masked thereby.

(4) Millar [16] writes, "Chlorpromazine induces mental calm, antagonises adrenaline and nor-adrenaline, is a powerful anti-emetic, potentiates anaesthetics, analgesics and hypnotics, and depresses excessive autonomic discharges."

(5) Several authors have commented on the drying up effect of chlorpromazine on the mucosae of the respiratory and upper alimentary systems. The value of this in the severe head injuries under discussion requires no emphasis.

(6) Fournel [17] showed that, in appropriate doses, chlorpromazine protected experimental animals against the stresses of oligaemic shock.

In brief, the writer's experiences of chlorpromazine with the cases in the major series of head injuries were as annotated below. These are in the form of clinical observations and impressions of sufficient occurrence as to be of significance.

Consciousness

This drug calmed overactivity of the cerebrum with appreciable depression of the level of consciousness, having a sedative effect on restlessness, both physical and mental. The level of consciousness could be assessed at any time without having to allow for sedative effects, and over-all it was far superior to paraldehyde and other drugs used for control of head cases. There was accelerated progress of improvement in the level of consciousness, particularly once such improvement had started. No physical restraint of the patient was required; the patients were nursed in adult cots and allowed freedom within the protective confines thereof.

Several of the cerebral contusion and laceration cases would adopt a hands and knees posture and remain so for periods, dosing or staring into space in a tranquil and docile state; they were of no trouble to themselves or the attendants. After a while they would curl up into a lateral foetal position and drowse peacefully. They would accept food and drink by spoon or feeder, with good co-ordinated swallowing, and when replete, tended to settle off and dose again. It was noticed that many of these patients became somewhat restless when the bladder was full and if they wet the bed. When this point was brought home to the attendant nursing staff they would watch for it and, on the provision of a urinal, the patient would often micturate normally and then lapse off into somnolence again.

Patients who developed the not uncommon traumatic epilepsy, without depression of the consciousness level between attacks (considered to be due to cortical venous thrombosis and usually manifesting itself about the third or fourth day), could often be controlled with the chlorpromazine alone and, if a combination of phenobarbitone and "Epanutin" had to be used, very small doses of these were necessary.

On recovering consciousness, many head injury patients, particularly those of higher intel-

ligence and those who were alcoholically intoxicated at the time of the accident, complain of "post-concussional headache" — usually generalised, but often localised—dizziness, loss of balance and awkwardness of gait and limb movements, sleeplessness, tendency to dose off and "coming to" with a mental and physical jerk, or worry on account of the amnesic period. They may also exhibit truculence, aggression, retiring weepy emotional behaviour, tendency to stay curled up in bed or, if made to sit up, they sit with a peculiar whining petulance, or disinterest in themselves or the environment. It should be explained that the writer believes that sitting up on a bed rest, sitting out of bed, ambulatory, physical and mental rehabilitation (including diversional and occupational therapy) are essential management therapies in these cases and they should be instituted as soon as possible. Rough clinical comparisons were made; and it was felt that patients who received chlorpromazine therapy at the earliest possible moment after injury either had none of the above-mentioned complaints or, if they had, they were minimal and fleeting. Patients who had the drug at later stages suffered proportionately more. Similar patients who did not receive the therapy until definite symptoms had developed usually lost these after four to seven days of 25 to 50 mg. orally every eight hours of chlorpromazine. Patients who sustained classical concussion of a degree sufficient to warrant ward admission to this busy and chronically overcrowded hospital, and were given early or medium early chlorpromazine therapy, had an average stay in hospital of 24 to 72 hours, seven days of 25 mg. orally twice daily of the drug at home before being medically discharged back to work.

Many patients who were admitted with severe cerebral contusion and/or laceration and were put on chlorpromazine statim (50 mg. intramuscularly every eight hours until able to take orally 25 to 50 mg.; a few cases who were very restless were given initial intravenous doses of 1 c.c. of the 2.5 per cent. solution diluted with 20 c.c. of normal saline at a very slow rate, with good effects), recovered in six to eight days sufficiently to go to the convalescent subacute wards, help in their own ward care, engage actively in physical and occupational therapies, etc. The length of the drug therapy during this rehabilitation period was variable, but the theme of the treatment was to stop the drug at the earliest possible moment. Despite the notorious peculiarities of the Bantu liver, there were no cases of complication of chlorpromazine in the series. The length of stay in the convalescent wards of these patients varied enormously, but the vast majority were discharged within four weeks. A small but noticeable residua remained in hospital for longer than four weeks, and it was noticed that, generally speaking, the improvement continued as long as they received the therapy. However, at the end of about four weeks the curve of recovery flattened off. When this was noted the writer stopped the drug and allowed natural reactions to continue the recovery. Review of some of these patients after six or more months was indeed gratifying. Many had recovered completely; others sufficiently so as to be useful and economic citizens; and others, who sustained arm or leg paralyses or pareses, usually showed early and complete leg recovery and gross recovery of the upper limbs, although the intricate hand/digit functions were often chronically impaired. These reviews are mentioned because it is obvious that brain recovery processes must and can occur naturally, and the only suggestion that the writer wishes to make is that chlorpromazine may be able to accelerate these normal processes.

It was also noted that patients with space-occupying chronic subdural haematomata did not lose their anxious facies or were their headache complaints more than slightly diminished when treated with chlorpromazine.

As time went on, several of the treated patients were able to fill in the gaps of knowledge during the amnesia periods before and after the accident. This was not due to subsequent discussions with family or friends, because many of the patients were "out of town" Natives who received no visitors. Many of the gaps were filled, with considerable detail, by memory, and others filled by the exercise of insight, deduction and comprehension. There is no doubt that this amnesia recession also occurs naturally in most head injuries, but it was felt that chlorpromazine accelerated the process.

The speech mechanism in the Bantu seems to be very vulnerable in head injuries, and several of the patients in the major series exhibited various types of aphasia. The speed of recovery of this serious deficit seemed to be greater in the chlorpromazine-treated patients.

The success of the therapy in these cases was not obtained in the small group of patients which form the subject of this paper. On the credit side, however, was the apparent prolongation of life, restoration of systolic, pulse pressure and diastolic readings to an approaching series

of normal ranges; hypersecretion was less troublesome and was held off for a longer period; metabolic processes seemed to be facilitated, and hyperthermic problems did not occur to any gross extent; but despite all these beneficial factors, the patients ultimately died. The writer does not feel that this necessarily vitiates the main theme of the management policy, but rather that the therapy just was not effective enough to reverse the changes and restore the central autonomic balance. Increasing the dosage of chlorpromazine did not influence the general trend of the progress of the cases. Perhaps another similar drug of greater potency and wider range of action may ultimately be the answer.

The writer gained the clinical impression that the perphenazine products, e.g., Trilafon, gave slightly better and faster results in the milder cases, but had little such influence on the progress of the more severe cases. The meprobamate compounds, e.g., Miltown, seemed to have no influence on the rate of recovery in any grades of head injuries.

"Opilon" (hydrochloride of acetoxy-thymoxy-ethyldimethyl-amine) was used in a few cases and was as successful clinically as chlorpromazine in the less severe cases, but no evidence was collected in the very severe head injuries.

SUMMARY

From the foregoing several important points emerge, and they are annotated below:

(1) The writer's stages of deficit in levels of consciousness give a much more practical clinical classification than the brief classical terms of mild confusion, severe confusion, semi-coma, coma, etc. The fundamental fallacy of the latter terms is the difference of opinion as to what the term actually denotes. The above-mentioned terminology ensures that a careful, complete, clinical assessment is made and the results are fully recorded in the clinical notes. If the patient is subsequently examined by the same clinician, or another using the same terminology, changes in the level of consciousness are thus able to be accurately compared.

(2) No clinician will quarrel with the emphasis which is laid on general nutrition and care of the respiratory system. It is obvious that the complications, due to neglect of the principles of management of these, are avoidable and should not happen.

(3) The suggestion that the injury forces cause "cerebral neuropraxia" and that this affects a traumatic neuronal discharge of both the cortical and the hypothalamus and associated brain stem cells, followed by a period of varying duration of non-return to resting phase, is a conception which is on less sure ground, though it must be somewhere near the truth. The speed of recovery of cells at both these cerebral levels depends on the local damage caused by the forces and thus the possible upset at the cell/pericellular medium interface. The fact that the brain has no lymphatics and no dynamic interstitial fluid circulation is indicted in the slow recovery.

(4) It is postulated that the recovery of both cerebral and hypothalamic cells depends first on the rapid recovery of the central sympathetic system (the normal reaction to bodily stress and injury) and then the resurgence of the central parasympathetic system until a true balance between these two opposing but complementary systems is obtained. If the central parasympathetic system (which is generally responsible for the restoration and maintenance of all bodily cells in a resting *status quo*) fails to emerge to the degree which will cause mobilisation of all the metabolic and humoral agents necessary to help the cerebral and tegmental cells to return to normal, then the uncontrolled sympathetic stress phenomena will continue until the patient dies in an exhausted state. The features of relatively high pulse, respiration and temperature readings, the raised blood pressure readings, the hypersecretion, etc., are interpreted as evidence of uncontrolled central sympathetic activity rather than vigorous manifestations of bodily compensations to impaired cerebral circulation and respiration of the gross type. The persistence of these features implies a failure of recovery of the central parasympathetic system and also a gloomy prognosis.

(5) Experiences with various "tranquillising" drugs in an attempt to effect the return to a balanced *status quo* in the hypothalamus are quoted. Although the results convinced the writer that chlorpromazine in particular achieved good results in the minor and medium severity head injuries, such success was not forthcoming in the group of cases forming the subject of this paper. However, it is felt that research along these lines can possibly supply the answer to the successful therapy of such patients.

(6) The qualitative similarity between the electrolytic exchanges of cerebral cell normal discharge and the results of electrolyte exchanges in the bodily cells as a response to injury should not go unnoticed.

(7) Purely hypothetical suggestions are made concerning the functions of the tegmental formatio reticularis. It is likewise suggested that these tissues suffer considerably in severe head injuries, particularly those with rotational and linear acceleration forces as their principal components. It is possible that dysfunction of these tissues leads to an inhibition of essential afferent information which the hypothalamus requires to maintain a balanced function.

(8) For the information of those clinicians who believe that the troubles of such patients are due to "cerebral oedema," it is interesting to record that such potent "oedema removers" as Diamox, Chlortride, triple strength blood plasma and hypertonic sugar solutions had no favourable effects in the few cases in which they were tried.

In conclusion, the writer realises that much of this paper is theory only and that "the mere bedside clinician has rushed in where physiologists fear to tread." However, if this paper only raises new interest, challenges the common fatalistic attitude and suggests a new line of approach towards the many problems of these severe head injuries, it will have achieved the writer's purpose.

The major series of head injuries referred to in this paper was investigated and recorded in the writer's surgical unit at Baragwanath Hospital (University of Witwatersrand), Johannesburg, South Africa. This non-European hospital, world famous for its abundance of pathology, receives an average of 5,000 head injuries per annum.

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