NEUROPLASTICITY AND REPAIR IN THE CENTRAL NERVOUS SYSTEM

Implications for Health Care

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1. INTRODUCTION

In 1977 the Thirtieth World Health Assembly decided that the main social target of governments and WHO should be the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life. In 1978 the International Conference on Primary Health Care adopted the Declaration of Alma-Ata, which stated that primary health care is the key to attaining the target of health for all by the year 2000.

Governments throughout the world are now developing and implementing primary health care as part of comprehensive national health systems. While primary health care is the fundamental component of health systems, these systems cannot be comprehensive, and primary health care cannot exert its full potential, unless there exist secondary and other levels of health care to support, and act as referral levels for, the primary level. These other levels will include hospitals and specialized facilities. Such facilities already exist in the developed countries, but are only slowly being built up in the developing countries.

One example of specialist facilities is neurosurgery, which is called upon to deal with such conditions as head injuries, hydrocephalus, cerebrovascular accidents, and tumours of the nervous system - all of which conditions are gradually increasing in frequency in the developing countries. With this situation in mind, the World Health Organization convened a scientific meeting on neuroplasticity and repair in the cerebral nervous system (Geneva, 28 June to July 1982). Neuroplasticity may be described as the capacity of cells of the nervous system to regenerate anatomically and functionally, after being subjected to developmental, environmental or pathological influences, including trauma and disease.

The meeting, which paid particular attention to the situation and needs of developing countries, reviewed existing knowledge on neuroplasticity, with special reference to the ability of the nervous system to recover from any kind of injury. The meeting examined methods for the evaluation of neural capacity to regenerate and establish adaptive functional connexions, of recovery of function mediated by surviving neurons and their pharmacological control, and of gains achieved through the elimination of factors interfering with normal function. It assembled available clinical and

psychometric information and looked at approaches to rehabilitation, and formulated new directives and strategies for field research studies in different cultures, and for the training of medical personnel. Finally, the meeting recommended appropriate innovative approaches to basic studies and clinical application, designed to evaluate nervous system recovery from injury and to provide guidelines for improving the care of persons with injuries to the nervous system, with special reference to developing countries. This publication is based on the deliberations of the meeting.

2. GENERAL PRINCIPLES

Definition and Scope

The boundaries of the scientific topic of neuroplasticity are broadened by the fact that the term can be used operationally to cover any of the adaptive mechanisms by which the nervous system restores itself towards normal levels of functioning after injury. Unquestionably, there are innumerable dynamic elements in the adaptive regulation of molecular, synaptic, and behavioural function which can be used by the nervous system to overcome clinical or experimental insults. However, neuroplasticity also has more explicit meanings when used to describe the series of steps by which specific injured central circuits attempt to repair themselves after injury and to restore function directly by the repair of the damaged circuits. It is in this connexion that one might perhaps hope for the application of innovative approaches to improve the care of persons with nervous system injuries in developing countries.

Neuroplasticity does not concern only the recovery of function if this latter is defined as "a return to normal or near-normal levels of performance, following the initially disruptive effects of injury to the nervous system" (Laurence & Stein, 1978). Neuroplasticity does not refer only to the structural and functional changes of the neuronal organization which follow an injury, but also includes the capacity of the central nervous system to adapt to new physiological conditions emerging either during its maturation or its interaction with the environment. Therefore, neuroplasticity consists in the ability of the nervous system to adapt (in both an anatomical and a functional sense) its structural organization to new situations emerging from developmental and environmental influences as well as from injuries.

For restitution of function after nerve tissue lesions, neuroplasticity may operate by means of synaptic reorganization, through either regenerative and collateral sprouting of axons or actual recruitment of potential pre-existing connexions. The latter may involve spared structures located in the affected area, i.e., intact structures temporarily excluded from their functional role which are capable of reassuming their functions. Alternatively, compensation phenomena may involve structures located in undamaged areas.

Basic Research[1]

Practical advances in this area cannot be expected in the absence of basic research. Such research is of necessity highly specialized and technical, involving the use of various experimental and pharmacological models for the study of the subject. It would not be appropriate to deal here in depth with the technicalities of this research, but it may be useful to the reader to list the lines along which investigations in this field are currently progressing.

In recent years, important research has been carried out on the following topics:

- synaptic connexions and transmitter systems
- the regenerative capacity of central neurons after experimental injury
- the immunocytochemistry of central neurons
- the regenerative capacity of central neurons as revealed by grafting experiments (stimulation of axonal regeneration by intracerebrally grafted target tissues; intracerebral implants to promote the bridging of regenerating central axons across lesions in the brain and spinal cord; reformation of severed connexions by intracerebral neural implants)
- monoamine grafts into the striatum (grafts of fetal substantia nigra; grafts containing peripheral dopamine cells)
- the effects of ganglioside treatment on the plastic responses of central neurons after deafferentation (recovery of nigro-striatal neurons; recovery of cholinergic and noncholinergic neurons in the hippocampus)

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[1] Details of this basic research are available to professionally interested persons. Inquiries should be addressed to: Neurological Disorders, Division of Mental Health, World Health Organization, 1211 Geneva 27, Switzerland.

- the capacity of the central nervous system for axonal regrowth (the growth of axons from recovery of the central nervous system into peripheral nerve grafts; the central origin of regenerating axons in the nerve graft; synapse formation after the regrowth of axons of the central nervous system)

- axonal elongation components (the fast transport component and axonal regeneration; the cytoskeleton and axonal regeneration)

- intermediate filament proteins (astrocytic filament and neurofilament proteins in peripheral nerve grafted to murine brain; fibrinolytic enzymes and regeneration of the central nervous system)

- in vitro models for neuroplasticity and repair (neuronotrophic factors; neurite-promoting factors)

- in vivo models to analyse neural regeneration

- in vitro development of dopaminergic neurons (mesencephalic neurons in primary culture; addition of striatal target cells in co-culture; the role of striatal cell membrane)

- humoral-chemical factors in the reorganization of interneuronal connexions (brain extract factors inducing postural asymmetry; postural factors carried in the cerebrospinal fluid; dynamics and properties of the cerebrospinal fluid and extract factors).

3. CLINICAL ASPECTS

Partly on the basis of the research referred to in the previous section, it is now possible for clinicians to pursue certain lines of action when dealing with patients suffering from conditions to which the phenomenon of neuroplasticity is relevant. These possibilities are outlined below, with particular reference to the developing countries.

Radiotracer Approaches for Studying Functional Recovery in the Brain

Single photon emission computed tomography

With positron techniques, the noninvasive measurement of regional cerebral blood flow and metabolism in man is limited to expensive and specialized instrumentation available in only a few facilities throughout the world. Pharmaceuticals labelled with commercially available single photon emitting radionuclides such as ^{123}I, ^{99m}Tc, or ^{111}In are, for the most part, not useful for evaluating cerebral blood flow or metabolism because of the peculiarities of the blood-brain barrier.

For non-ionic substances without a specific transport mechanism, the penetration rate from the blood into the brain is directly related to lipid solubility. For example, ethyl alcohol, which is lipid-soluble, has a considerably greater rate of uptake than thiourea with a very low lipid solubility. In general, these lipophilic substances pass from the blood to the brain by passive diffusion, unaffected by the barrier mechanisms. Because lipid-soluble material such as oxygen, carbon dioxide and the inert gases such as ^{133}Xe penetrate the blood barrier passively, there is rapid equilibration.

Amines

Radiolabelled amines, such as ^{123}I-iodoamphetamine, are lipophilic compounds which are extracted by the brain in proportion to the blood flow (Winchell et al., 1980; Kuhl et al., 1981). Scintigraphic maps of regional cerebral blood flow can therefore be obtained using commercially available radionuclides and standard single photon emission computed tomography instrumentation.

The initial distribution of iodoamphetamine correlates with regional cerebral blood flow (Lear et al., 1982).

There is a good agreement between regional cerebral blood flow values based on the iodoamphetamine distribution and blood flow measured by autoradiography using ^{14}C-iodoantipyrine. Over a range of 20 to 300 ml/100 g/min flow, the correlation between flow as measured by iodoamphetamine and iodoantipyrine are the same.

At present emission computed tomography is being performed using single photon emission computed tomography after the intravenous injection of n-isopropyl ^{123}I-p-iodoamphetamine[1] in patients to evaluate their regional cerebral perfusion (Hill et al., 1982).

For patient studies, at least one tomographic image is obtained at 2 cm above the orbitomeatal line. Additional images are obtained at 2 cm increments from the initial slice. The injected dose is 185 MBq (5 mCi), and imaging is performed between 20 and 60 minutes after the injection.

When ^{123}I-iodoamphetamine is injected intravenously, the dose is initially deposited in the lung. Maximal lung uptake is achieved between 1 and 2 minutes, with a fairly rapid washout from the pulmonary compartment. Brain activity is observed 30 seconds after injection and is greater than 80% of peak activity by 2 minutes. Brain activity remains constant from about 20 minutes to 60 minutes after injection, with 6-9% of the injected dose deposited within the brain parenchyma.

Patients without disease of the central nervous system and with normal computed tomography examinations demonstrate bilaterally symmetrical activity on the ^{123}I-iodoamphetamine images. Activity is greatest in a strip of cortex along the convexity of the frontal, temporal, parietal, and occipital lobes, corresponding anatomically to cortical grey matter. Activity is also high in the region corresponding to the basal ganglia. The region between the basal ganglia and the convexity corresponding anatomically to cortical white matter shows less iodoamphetamine activity. The activity in the cortical grey matter is uniform in the temporal, parietal, and occipital regions but appears patchy in the frontal region. The contour of this activity is undulating and reflects the gyral architecture observed on

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[1] Medi-Physics Inc., 5855 Christie Avenue, Emeryville, CA 96408, USA.

the computed tomography examination. Depressions due to the interhemispheric and Sylvian fissures are also present.

The recent development of single photon emitting radiopharmaceuticals such as ^{123}I-iodoamphetamine which are rapidly extracted by brain and distributed according to cerebral blood flow (Winchell et al., 1980; Kung & Blau, 1980) offers the potential for longer data collection periods and therefore higher spatial resolution. This potential has been realized in several studies in patients with stroke (Hill et al., 1982) and epilepsy (Magistretti et al., 1982). The rapid localization of the iodoamphetamine permits accurate measurement of regional cerebral blood flow, even when flow is stable for only several minutes. This is an important advantage especially when studying transient phenomena such as occur in epilepsy or under the influence of physiological stimulation. The higher resolution also allows a smaller volume of brain to be sampled. As a result, the discrete, focal changes in regional flow seen during physiological stimulation can be measured.

The flow patterns associated with stroke have been well defined (Hill et al., 1982). Areas of cerebral infarction appear as regions of markedly reduced cerebral blood flow, sometimes with peripheral zones of increased flow. Remote areas of cerebral cortex and regions with significant afferent input from the infarct zone may also manifest reduced flow. The area of reduced cerebral blood flow on single photon or positron tomography is usually more extensive than the area of abnormality on transmission computed tomography. Thus the functional abnormality is greater than the area of cell death.

In applying emission tomographic studies of regional cerebral blood flow to the evaluation of neuroplasticity following stroke, it is important to understand the concept of the penumbra (Astrup et al., 1981) surrounding the area of cell death. When cerebral blood flow falls below 15-17 ml/100 g per minute there is a loss of electrical activity. However, the cells are largely intact metabolically when the flow is above 10 ml/100 g per minute and will return to normal if flow is restored. A blood flow of 15-17 ml/100 g per minute can therefore be thought of as the electrical threshold, as all cells receiving less than this flow will be electrically silent and their function will be abnormal to clinical testing. Below 10 ml/100 g per

minute, the metabolic threshold, there is a failure of cell metabolism with consequent irreversible changes leading to cell death.

The study of blood flow changes associated with learning and rehabilitation may also shed light on the gross distribution of functional interconnexions between neurons in different parts of the brain and possibly give data on the known wide distribution of memory function. This knowledge may point to specific rehabilitation strategies likely to produce successful relearning of certain functions by different areas of the brain. Perhaps studies of regional cerebral blood flow will eventually be used in patients after stroke as predictors of who will benefit from rehabilitation and which particular programme of rehabilitation is most appropriate for the individual patient.

Application to developing countries

In developing countries, the priorities for health care spending are more oriented towards primary care. However, if a relatively inexpensive technique could be developed to assess the likelihood of recovery after stroke, the long-term savings yielded by concentrating the rehabilitation effort on those patients in whom functional takeover by non-affected areas is found to be possible, would be considerable.

The incidence of cerebrovascular diseases in developing countries is very high but the long-term social effects of these diseases are not as striking as in industrialized countries. As urbanization progresses, the social problem of the placement of stroke survivors will become increasingly important. Therefore, it is crucial for those countries to address the problem ahead of time, and to start preparing the investigative and therapeutic infrastructure.

It seems clear now that expensive techniques such as positron emission tomography, in spite of its potential, will never be a realistic option for a national health care programme in a developing country. The research effort and the contribution of international organizations concerned with developing countries should be centred on the development of single photon techniques, as these are the only ones that have the potential of being introduced in these countries in the foreseeable future.

Extracranial to Intracranial Anastomosis and Repair

Rationale

The surgical procedure of extracranial to intracranial anastomosis is aimed at providing the blood supply to the ischaemic area of the brain, by bypassing the occluded vessel. Though this concept was suggested by Fisher in 1951, the technical possibility was not evolved until 1967 (Donaghy, 1967). The superficial temporal artery is anastomosed to a branch of the middle cerebral artery on the side of vascular occlusion. In a few instances the occipital artery is also used, depending on the site of the lesion and condition of the superficial temporal artery. The regional blood flow studies in animals (Fein & Molinari, 1974) and in man (Murray, 1978; Little et al., 1979) have clearly shown that the anastomoses increase the blood circulation to the affected ischaemic area. The clinical results of this procedure, including the mortality and morbidity from different centres, have been reviewed (Kletter, 1979). The mortality rate of this procedure (i.e., deaths within 30 days of the operation) is about 3.5%. The overall morbidity rate depends on the clinical condition of the patient. In recent years, this procedure has found wide acceptance as a useful method of treatment, as a preventive measure in transient ischaemic attacks, and for recovery in some cases of completed stroke.

Collateral potential exists at a number of anatomical vascular levels, from the great arteries supplying the brain to the smallest vessels of the microvascular bed of the cortex and white matter (Feindel et al., 1979). The collateral circulations include the extracranial to intracranial via the ophthalmic artery or middle meningeal to cortical vessels, the circle of Willis, and anastomoses joining the three major anterior, middle and posterior cerebral arteries. In addition, more distally, the branches of cortical vessels form a capillary network. Through these vascular anastomoses at different levels, the collateral and retrograde blood flow is established when one or more major vessels are occluded.

Using fluorescein angiography, the retrograde collateral flow has been shown responsible for perfusion flow in the cerebral microcirculation (Feindel et al., 1967). The anatomical presence of these collaterals does not necessarily mean that they are always functionally effective. This

depends very much on the haemodynamics, time factor and size of the anastomoses. Only when the collaterals fail to replace the lost blood flow, or when the replenishment is delayed, do the clinical features of neurological deficits appear. If the collateral circulation is established from the neighbouring cerebrovascular bed, the clinical deficits will recover. Sometimes recovery may be due to modification of the neuronal metabolism so that the function may be resumed at a lower basal level of blood flow.

The neuron in vivo depends mainly on the oxidation of glucose for its energy metabolism which maintains the normal functioning of ion pumps. Since the brain does not store glucose and oxygen the neurons depend solely on the continuous cerebral blood flow. The ischaemic brain shows a dense central infarcted area where the blood flow is below the lower critical level of 0.10 ml/g/min. This will be surrounded by an area where the blood flow is greater but inadequate to maintain electrical functioning of the neuron. These areas have been shown by means of microelectrode observation of somatosensory evoked potentials in the baboon cortex (Branston et al., 1974). The electrical response was maintained at the levels of 18-20 ml/100 g/min, while at levels below 10-12 ml/100 g/min the response was absent. In the area of 14-16 ml/100 g/min there was a very sharp decline of the electrical activity. This observation was confirmed by Heiss et al. (1976). In this condition, the residual perfusion supplies sufficient oxygen to maintain close to normal tissue concentration of ATP, so that cell energy metabolism is continued at a low level.

This type of moderate energy imbalance does not lead to neuronal damage. Symon & Astrup (1979) have developed the concept of ischaemic penumbra for this area of electrical silence with neuronal structural integrity.

In short, the pathophysiological changes in ischaemic brain are a zone of central infarction where cellular disintegration has occurred, surrounded by a zone of ischaemic penumbra where the neurons are functionally inactive but structural integrity is maintained while cerebral blood flow does not fall below the critical threshold of 0.10 ml/g/min. Depending on the size of infarction with the loss of cellular metabolism and ion homeostasis, brain oedema will be associated. If the infarct is small with a zone of electrical silence, the transient neurological deficits will recover with the

formation of collateral retrograde flow. This is seen in transient ischaemic attacks. If the occlusion is complete in one of the major vessels, the area of infarction may be wide enough to produce gross structural damage, resulting in neurological deficits.

Role of extra- intracranial anastomosis

The purpose of this revascularization is to increase blood flow to the affected ischaemic brain. Simple restoration of circulation alone may not reverse the dysfunction of ischaemic brain. This is because of various factors that complicate the ischaemic condition, such as associated cerebral oedema and haemodynamic and metabolic disturbances related to post-ischaemic hypoperfusion and hypermetabolism. The no reflow phenomenon resulting from changes in blood viscosity and vascular endothelial changes associated with brain swelling may impair the formation of collateral circulation and anastomosis may fail. Therefore, the role of revascularization in the prevention and treatment of stroke depends upon two factors which play an important role in determining the onset and evolution of cerebral infarction (Conforti et al., 1979): (1) the compensatory effect of the collateral circulation, and (2) the recovery of neuronal metabolism in reversible cerebral ischaemia.

Indications for extra- intracranial anastomosis

This procedure is mostly effective in preventing impending stroke rather than as a therapy in completed stroke. The best results are obtained in patients with transient ischaemic attacks, reversible ischaemic neurological deficits, and partial non-progressing strokes. The benefit in progressive and completed strokes is doubtful. Recently functional investigations, such as regional cerebral blood flow measurements and fluorescein angiography combined with direct measurement of perfusion flow from multiple cortical areas using positron emission tomography, are being used to improve the selection of patients (Feindel et al., 1979). If regional blood flow measurements show either normal or severely low values, the anastomoses may not be beneficial. The most suitable patients are those with focal reduction with normal or decreased mean blood flow. In acute strokes, the anastomosis is contraindicated. Its beneficial effect in completed strokes and in long-standing neurological deficits is very doubtful.

Recovery

Clinical recovery in certain selected groups of patients with stroke after revascularization is well known. However, at present there are no randomized clinical trials comparing the results in patients who underwent extra- intracranial anastomosis with the results in patients managed with medical therapy alone or those in patients whose disease followed its natural course. The results of a collaborative randomized study currently being conducted (Barnett et al., 1980) should provide useful data on the effectiveness of by-pass surgery in stroke.

However, it is a common experience of physicians that certain patients do recover after stroke, although the mechanism whereby this occurs is not clear. Morphological and biochemical changes at the cellular and synaptic levels may be involved. The role of growth factor in cellular regeneration and restitution is being studied. Butters (1974) has introduced the concept of resilience of function after multi-stage lesions of particular cortical foci in adult monkeys. The recovery in transient ischaemic attacks, with or without revascularization, may not be merely reactivation and restitution of cellular function in the ischaemic penumbra. The resilience of neuronal function may be responsible for recovery, but the mechanism and mode of this resilience is still not understood.

Though fundamental research work has established the existence of the sprouting mechanism in the central nervous system, the basic question raised by Schneider in 1973 whether this is functional, and if functional whether it is useful, has still to be answered. Lashley's theory of equipotentiality and Rosner's theory of redundancy have yet to be reviewed and confirmed. Further, Lishman, Wall and others have raised the possibility that late mechanisms are responsible for long-term intellectual gains by patients after stroke (Wall, 1971). New connexions, reroutings or reorganization may be effective, and possible morphological changes both at pre- and post-synaptic levels may give rise to previously non-existent or ineffective connexions to produce functional recovery.

Lastly, the influence of rehabilitation in retraining the individual to regain functions needs to be elucidated. Neuroplasticity in vascular occlusive conditions may be related to the ability of the central nervous system to adapt to the new environmental situation.

The starved struggling neurons are helped by revascularization procedures like extra- intracranial anastomosis to cope with the new demands and achieve functional recovery.

Omental Transplantation to the Brain

In 1979, Goldsmith et al. first reported on the topic of "omental transposition to the brain of stroke patients". The operative results of three patients with cerebral ischaemic disorder were encouraging. Since then, this procedure has been practised in various parts of China (71 cases in ten medical units).

Surgical procedures

Two different operative methods were used. In the first, intracranial transplantation of omentum with pedicle, the omentum was well tailored and lengthened and brought out of the peritoneal cavity, and the elongated omentum, which was fed by the right gastroepiploic artery, passed through a subcutaneous tunnel to the craniotomy area. In the second, intracranial transplantation of free omentum, a part of omentum was cut down, and the blood vessels of the free omentum were anastomosed with one of the following pairs of vessels: superficial temporal artery and vein, superior thyroid artery and superior temporal vein, external maxillary artery and vein, or external maxillary artery and superficial temporal vein.

The surgical results were evaluated as follows: (1) cases recovered (neurological deficits and symptoms disappeared); (2) cases markedly improved (the muscle power of the paralysed limbs improved more than 2 degrees); (3) cases improved (the muscle power of the paralysed limbs improved not nore than 2 degrees); or (4) no effect (no improvement in neurological symptoms or deficits).

The post-operative complications were: subcutaneous infection (two cases), generalized epileptic attack four days after operation (one case), and subcutaneous effusion in the tunnel (one case). There were no deaths in this series.

The study confirmed that improvement is obtained in the treatment of cerebral ischaemic diseases with the method of omental transplantation (transposition).

Owing to the abundant vascularization of the omentum it is possible that this intervention enhances the local vascular perfusion, and in a few cases neurological improvement appeared within the 24 hours of the surgical intervention. Goldsmith considered the possibility of biochemical involvement in order to explain the effectiveness of this surgery. The most dramatic recent advances in neurobiology have been the recognition of the importance of peptides as neurotransmitters and neuromodulators in the central nervous system and in peripheral and autonomic nerves. It is known that peptides considered until now confined to the gastrointestinal tract demonstrate specific biochemical activities at central nervous system level. It was recently proposed that vasoactive intestinal polypeptides may play a regulating role in the local control of energy metabolism in mouse cortical slides (Magistretti et al., 1981).

The characteristics of the two surgical approaches may be compared as follows. For pedicled omentum transplantation, (1) anastomosis of the vessels is not needed and it is easy to get adequate blood flow, (2) a long subcutaneous tunnel is required and post-operative strangulation of the omental pedicle may occur, (3) the procedure is simple and needs no special equipment, and (4) the omentum must satisfy certain conditions, which often constitute an important factor affecting the operative procedure. For free omentum transplantation, (1) anastomosis of arteries and veins is needed and blood flow is comparatively inadequate, (2) a subcutaneous tunnel is not needed or is only located on the head and neck and no strangulation of the omental pedicle occurs, (3) anastomosis of the arteries and veins requires skilful technique and an operating microscope is indispensable, and (4) the conditions required for the omentum transplantation are not very strict, and generally they do not affect the result of the operation.

With the popularization of microsurgery and progressive improvement in techniques for anastomosing vessels, free omentum transplantation is being increasingly used. The choice of blood vessels used for anastomosis has been expanded from superficial temporal artery to superior thyroid artery and external maxillary artery. Experience to date indicates that free omentum transplantation is more effective than pedicled omentum transplantation.

The study has shown that omentum transplantation is a feasible, safe and effective method for the treatment of cerebral ischaemic diseases. Further studies to understand the basic mechanisms involved are however needed.

Cerebrospinal Fluid Shunts: Anatomical Repair and Functional Recovery

Extracranial diversion of the cerebrospinal fluid to the blood or body cavities is the preferred method of treating most cases of non-tumour hydrocephalus and cases of tumour hydrocephalus that are not amenable to direct operation.

The operative mortality of these shunting procedures is very low (1-2%), but late complications frequently occur and repeated revisions are often required to accommodate growth and to correct late complications. The major complications are shunt obstruction, shunt infection and thromboembolism (Massarotti et al., 1969, 1971).

Pathological findings in the hydrocephalic brain

Developmental anomalies tend to reflect both the primary effects of increased intraventricular pressure and the secondary effects of ventricular enlargement.

Many factors, such as the age of the patient, the expansibility of the skull, and the duration of the syndrome, may greatly modify the influence of the hydrocephalus on cerebral tissue.

The lateral ventricles are the first to dilate because they are surrounded by the least structural resistance.[1] The frontal and occipital horns expand readily, while the temporal horns and bodies of the lateral ventricles are slower to enlarge.

The third ventricle and the aqueduct of Sylvius are the least expansive segments of the ventricular system.

The fourth ventricle tends to enlarge posteriorly into the less resistant tissue of the cerebellum and, in certain congenital conditions (e.g., atresia of foramina of Luschka and Magendie) may become very large.

Ventricular enlargement stretches the ventricular surface and pogressively produces a disruption of the

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[1] Hammock, M. K. & Milhorat, T. H. Experimental obstructive hydrocephalus. Part I, The primate model. Paper presented at the Symposium on Cisternography and Hydrocephalus, Washington, DC, 1971.

ependymal epithelium, with dilatation of the intercellular clefts and oedema of the subependymal tissue (Weller & Wisniewski, 1969).

With severe progressive enlargement the septum pellucidum is reduced to a narrow membrane and may completely disappear.

Hydrocephalus thins and distends the brain parenchyma. The vertex and occipital lobe show greater mantle thinning than the frontal regions (Epstein et al., 1977). The main finding is white matter atrophy, restricted in less severe cases to the periventricular zone. The effect of severe hydrocephalus on the size and number of brain cells has been investigated in hydrocephalic animals: it is concluded that the ventricles can expand without significant cellular loss. Nevertheless, the axons in the periventricular white matter become elongated with disruption of the surrounding myelin This event, and not the loss of brain cells, may be a factor limiting repair of cerebral damage (Rubin et al., 1972).

It is noteworthy that myelination of the corpus callosum is also greatly delayed (Gadsdon et al., 1978).

Histologically there is a reduction in the number of astrocytes and oligodendroglial cells (Blackwood et al., 1963).

A highly characteristic finding in all forms of hydrocephalus is the preservation of the grey matter even in very advanced cases (Blackwood et al., 1963). Thus the major atrophic process in hydrocephalus probably involves the neuroglia and axonal collaterals rather than the neurons and main axonal trunks, until end stages of the disease are reached (Penfield & Elvidge, 1932).

Alterations in general brain function

Hydrocephalus produces a wide range of alterations in brain function, related both to increased intracranial pressure and to the specific effect of ventricular enlargement on cerebral tissue (Milhorat, 1972). Circulatory disturbances and reduction of cerebral blood flow must also be taken into account.

Mental and motor disturbances have been widely reported, such as paresis, spasticity, visual defects, and specific

alterations of electroencephalographic patterns, of visual and auditory evoked potentials (De Vlieger et al., 1981) and of the endocrine system (Milhorat, 1972).

Data obtained in experimental animals and humans indicate that hydrocephalus greatly impairs the function of the blood-brain barrier, interfering with the transport of substances between the blood, the cerebrospinal fluid and the brain.

In congenital non-communicating hydrocephalus ^{24}Na injected into the ventricles disappears from cerebrospinal fluid over a very long period of time, indicating an impairment of transependymal reabsorption (Migliore et al., 1964).

Increased levels of acid monoamine metabolites have been demonstrated in the cerebrospinal fluid of hydrocephalic children (Andersson & Roos, 1969; Massarotti et al., 1978). The increase, according to experimental evidence in animals, seems related to a disturbance of metabolite transport mechanisms from the fluid to the blood (Massarotti et al., 1974).

Study of the quality of life in hydrocephalic children has been stimulated by improved methods of surgical treatment.

Studies of children with hydrocephalus have focused on cognitive development and on the level and pattern of intelligence in relation to various parameters and symptoms (Dennis et al., 1981).

Others (Dorner, 1976; Connell & McConnel, 1981) have looked at the social and emotional adjustment of affected children and at the risk of developing psychiatric sequelae.

Some efforts have been made to correlate global and regional cortical thinning with subsequent intelligence (Young et al., 1973; Dennis et al., 1981). It has been demonstrated that no consistent correlation exists between cortical thickness and the eventual development of mental and motor skills (Laurence & Coates, 1962). However, many authors agree that a cerebral mantle of 2 cm or more is generally associated with a good prognosis, while 1 cm or less indicates a poor prognosis (Matson, 1969; Castro-Gago et al., 1979).

Recently, it has been demonstrated that, if the degree of the whole cortex or regional thinning is a poor predictor of subsequent intelligence, selective abnormalities in the posterior regions of the brain (vertex and occipital lobe) appear to be associated with poorer development of non-verbal as compared with verbal intelligence (Dennis et al., 1981). Association with ocular abnormalities, motor deficits and seizures may determine an uneven growth of intelligence during childhood.

Effects of successful shunting treatment

A successful shunting procedure often restores the ventricular system to normal size, reconstitutes the cortical tissue and allows normal myelination of the corpus callosum (Rubin et al., 1975).

Nevertheless, many of the histological changes seen in the cortical tissue before the operation may remain. Moreover, especially in non-communicating hydrocephalus, the asymmetry of anteroposterior cortical-mantle thinning, depending on the fact that the vertex and occipital lobe are thinner than the frontal lobe, may persist and affect the pattern of intelligence during childhood.

It is well known that hydrocephalus (especially communicating cases) may spontaneously arrest: continued damage to the brain ceases, the pressure of the cerebrospinal fluid returns to within normal limits, and neurological signs and symptoms disappear. Clinically, arrested hydrocephalus is manifested by progressive development of mental and motor function. The recovery depends on the extent of cerebral damage caused by the primary illness and secondary ventricular dilation.

Surgery of Head Injuries in Developing Countries

Head injuries constitute a large part of the professional responsibilities of neurosurgeons, especially those working in the developing countries. Traffic accidents, domestic injuries, assaults, occupational and industrial accidents and other sources provide the cases, each causative factor being influenced by the socio-cultural characteristics of the particular country (Adeloye, 1980). Thus, falls from trees in Africa (Ebong, 1978) and train accidents in India (Kalyanaraman & Ramamurthi, 1969) contribute their quota of craniospinal injuries. Males are more susceptible to head injuries than females; about

one-third to one-half of patients with head injuries in the developing countries are under the age of 15 (Adeloye, 1980).

Incidence of surgical management

In a series of 525 consecutive cases of head injuries seen at the University College Hospital, Ibadan, Nigeria, in a six-month period, only five underwent emergency neurosurgical operation (Adeloye et al., 1976). In another series of 4000 cases of head injuries, both of acute and chronic nature, seen at the same hospital in a seven-year period, 142 (3.5%) underwent neurosurgical operation (Olumide & Adeloye, in press).

In India, of 600 consecutive cases of head injuries admitted to the Government Hospital, Madras, in one year, 89 (nearly 15%) underwent surgical treatment (Kalyanaraman & Ramamurthi, 1969).

Indications for surgery

In Ibadan, Nigeria (Olumide & Adeloye, in press) the commonest indication for surgery in head injury was found to be confirmed or suspected intracranial haematoma (73% of cases). Next in importance was compound depressed fracture (22%). Rare indications for surgery included repair of skull defect, repair of growing skull fracture, suturing of major scalp laceration, elevation of a closed depressed fracture, and excision of a calcified subgaleal haematoma.

In India, the commonest indication for surgery in adults was found to be intracranial haematoma (Kalyanaraman & Ramamurthi, 1969). The haematomata found, in order of frequency, were the subdural, extradural and intracerebral varieties. Elevation of depressed fracture was the commonest indication for surgery in Indian children seen in Madras. Other indications for surgery included persistent cerebrospinal fluid rhinorrhoea and exploration of the optic chiasm for post-traumatic blindness.

El-Gindi et al. (1979) described other vascular complications of head injuries for which surgical treatment was carried out in Egypt.

Extradural haematoma

Three varieties of this important complication of head injuries have been recognized.

Acute extradural haemorrhage. This is due to arterial bleeding. The incidence reported in the developing countries varies because of poor documentation. An incidence of 1% of extradural haematoma was recorded in Cairo (El-Gindi et al., 1979). The impression is that the reported cases underestimate the true incidence of this disease since if not promptly treated surgically the patient dies without reaching hospital. Besides the classical picture of initial concussion, followed by a lucid interval, unconsciousness and neurological deficits occur in about 25% of cases in Egypt.

The treatment is surgical, consisting of emergency burr hole evacuation of the haematoma and arrest of bleeding.

The mortality is high, ranging from about 30% in Kenya (Luther & Ruberti, 1976) to 50% in India (Kalyanaraman & Ramamurthi, 1969). The best results are achieved if surgery is performed before the development of bilateral dilated fixed pupils or the decerebrate state. Associated brain damage accounts for the high mortality, the damage being more in head wounds caused by road traffic accidents than those sustained in assaults.

Chronic (delayed) extradural haemorrhage. In this form, there is delay in the evolution of the disease. The source of the bleeding is venous. Glassaeur (1976) commented on its relatively common occurrence in Zimbabwe; years before however cases of "atyical extradural haematoma" were reported in South Africa (Sartorius & Humphries, 1946). Isolated cases were reported in Egypt (Tawfik, 1976) and Nigeria (Adeloye & Onabanjo, 1980). A series of 13 cases in 10 years occurred in Cairo, Egypt.[1] Some of these cases were first diagnosed as post-traumatic headache or subdural haematoma. Computed tomography is useful in the diagnosis of delayed extradural haematoma.

Surgical removal of the haematoma is the only useful treatment. The prognosis after operation is very good and most patients recover completely.

Sagittal extradural haematoma has been well described by El-Banhawy et al. (1971) from Egypt. The diagnosis is

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[1] Salama, M. Delayed extradural haematoma. Paper presented at the Fifth Annual Ain Shams Medical Congress, Cairo, March 1982.

difficult because of little assistance obtained from carotid angiography. Three types of this disease are recognized from clinical and angiographic findings.

The frontal type is the mildest form and may be managed conseratively if the headache gradually abates as the haematoma resorbs. Usually the haematoma persists and the headache worsens; surgical treatment then becomes necessary. A single midline burr hole in front of the coronal suture and behind the hairline is curative.

The parietal variety is treated by four burr holes, two on either side of the midline.

The occipital lesion is the least common but the most severe. The haematoma may extend to the posterior fossa, with dangerous consequences. Treatment is by multiple burr holes in the occipital bone.

Subdural haematoma

This complication of head injury is of medical and surgical interest. Every doctor should recognize it and solicit surgical management, especially for the chronic variety, since the results of operative treatment are very good.

Subdural haematoma occurs more frequently than extradural haemorrhage. Nevertheless, the ratio of documented cases of extradural to subdural haemorrhage is variable - 1:20 in Ghana (Mustaffah, 1976), 1:7 in Kenya (Luther & Ruberti, 1976), 1:4 in Egypt (ElGindi et al., 1979), and 1:2 in India (Kalyanaraman & Ramamurthi, 1969).

Three types are recognized, namely, acute, subacute and chronic subdural haematomata. The acute disease presents within 3 days of wounding, the chronic variety presents after 3 weeks, and the subacute presents between 4 and 21 days after the injury. In a series reported from Ibadan, Nigeria (Odeku & Idowu, 1967) there were 5, 7 and 13 cases of the acute, subacute and chronic disease, respectively.

Acute subdural haematoma is a serious disease with a mortality of from 50% to 80%, due to concomitant severe brain damage.

Exploration and drainage of the haematoma through bilateral burr holes is the usual surgical treatment. The

mortality remains high nevertheless, even in parts of the world which have sophisticated supportive measures.

Subacute and chronic subdural haematomata have a much better prognosis than the acute disease. Chronic subdural haematoma is the single commonest vascular complication of head injury in Cairo, Egypt (El-Gindi et al., 1979). Over six years, Ohaegbulam (1981) encountered 132 patients with post-traumatic subacute and chronic subdural haematoma in Enugu, Nigeria.

There is a striking male preponderance in these lesions, especially in patients below the age of 45 years. The age distribution and clinical presentation in developing countries are comparable to what has been observed elsewhere (Ohaegbulam, 1981).

Treatment by evacuation of the haematoma through bilateral burr holes gives very good results in most cases. In Ohaegbulam's series the outcome of this simple surgical procedure was described as excellent in 62% of cases; 33% had mild disability and 4% remained disabled. There was only one death.

Intracerebral haematoma

Post-traumatic intracerebral haematoma is encountered less frequently than subdural and extradural haematoma. The report from Egypt (El-Gindi et al., 1979) showed the following distribution: subdural 71%, extradural 17%, and intracerebral 12%.

Diagnosis by angiography is not satisfactory. The results of surgery are poor, the mortality being about 40%.

Skull fractures

Compound depressed fracture is an important and common indication for surgery in head injuries. Assaults constitute an important source of this fracture. If it is inadequately treated, infection supervenes. Indeed, in the developing countries many cases of intracranial abscess follow head injury.

The surgical treatment of compound depressed fracture is débridement with elevation of intact depressed bone and removal of loose comminuted fragments. The dura is repaired. The post-operative results of this conventional

surgical treatment are very good (Adeloye et al., in press). Volo of Uganda recommended immediate replacement, and not removal, of the loose bone fragments.[1] This technique, he claimed, does not cause any more infection than when the fragments are discarded. In addition, immediate bone replacement removes the need for the subsequent major operation of cranioplasty.

Simple depressed fracture is much rarer in its incidence than the compound variety. Conservative treatment usually suffices. Surgery is indicated for cosmetic reasons and when there are unrelenting features of irritation and compression of the brain. The results of surgery are excellent (Adeloye et al., in press).

Growing skull fracture is an unusual complication of head injury in infancy and childhood. It is characterized by (a) parietal skull fracture, (b) dural laceration which exposes the leptomeninges, and (c) subsequent enlargement of the fracture due to pulsating hernia of the leptomeninges. Radiologically, the typical features of the disease are progressive widening of the fracture and scalloping of the inner table of the skull bordering the fracture.

Goldstein et al. (1970) described three varieties of the disease; Adeloye (1971a) added a fourth type.

The disease is very rare, and isolated case reports occur in literature (Lende & Erickson, 1961). In the developing countries, cases have been reported from Egypt (Higazi, 1963) and Nigeria (Adeloye, 1971b).

The usual surgical treatment consists of repair of the dura with or without cranioplasty. The pulsating swelling is usually cured but not the neurological deficits due to pressure atrophy of the brain.

Penetrating head injuries

Penetrating head wounds inflicted by missiles are usually treated like compound depressed fractures. Débridement is carried out, with the removal of indriven

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[1] Volo, G. B. Immediate bone replacement in compound depressed fractures of the skull in Mulago Hospital. M. (Med.) (Surgery) dissertation, Makerere University, Uganda, 1975.

bone, metallic fragments, other foreign matter, haematoma and necrotic brain tissue along the wound track. The results of surgery are satisfactory, the early results obtained depending on the brain damage caused by the missile.

The tangential skull wound in which bone fragments, not metallic ones, are driven intracranially should be treated with care. It is not enough merely to suture the scalp wound. Failure to remove the indriven bone fragments during surgical débridement usually leads to infection and epilepsy (Adeloye, 1978).

Retained metallic bodies are often well tolerated by the brain. When, however, the retained bodies move within the intracranial cavity, they should be removed. Copper- and nickel-plated missiles tend to cause a sterile and substantial abscess, whereas lead bullets induce little reaction. The bullet subsequently moves in the abscess cavity produced. Movement is also aided within a natural space such as the ventricular system.

The head can be positioned in a way that will help gravity to move the bullet to a position where it can be surgically removed. Stereotaxic surgery has also been employed in this exercise (El-Shafei et al., 1973). The operative results are usually satisfactory.

Facilities for surgical treatment

In an Ibadan, Nigeria, series (Olumide & Adeloye, in press), only 7% of patients with head injuries had negative findings at surgery. This implies that with the short supply of neurodiagnostic facilities, neurosurgeons working in developing countries must rely a great deal on their clinical judgement in selecting patients with head injuries who need surgical treatment. To assist such surgeons, centres of neurosciences should be established in the developing countries. Such places will be able to afford the more sophisticated neurodiagnostic equipment, for example, the computed tomography scan. Neuroscientific manpower can also be pooled at such centres, not only to improve neurosurgical care but also to provide training in local disease entities. In Ibadan, less than 5% of patients with head injury underwent surgical treatment. This is much lower than the nearly 15% recorded by Alexander in England and also at the Madras Institute of Neurology and Neurosurgery. It thus appears that the differences in the use of surgical treatment in head injury observed between

geographical parts of the world may not be due to disease entities but are the expression of the availability (or non-availability) of neurosurgical manpower and diagnostic facilities.

Recovery after Surgery in Chronic Spinal Cord Compression

Spinal cord tumours

Chronic spinal cord compression can be secondary to several etiological factors: tumours of the spinal cord itself, tumours that arise and are located in the bones of the spinal canal or in the elements surrounding the spinal cord (roots, meninges, dura madre, vessels), and also some parasitic diseases such as cysticercosis, or infectious disorders such as Pott's disease.

Spinal cord tumours are less frequent than the intracranial tumours in a variable proportion of 1:4 according to Kurland (1958), 1:4 according to Kernohan et al. (1931), and 1:7 among 1000 tumours from the Instituto Nacional de Neurología de México (F. Escobedo, personal communication, 1982); and spinal cysticercosis corresponds to 1% of all the "neurocysticercosis" cases.

The neurinomas derived from the spinal roots, the meningiomas derived from the meninges surrounding the spinal cord, as well as certain cysts of cysticercosis, constitute a "chronic pathology", histologically benign, slow-growing, out of the spinal cord, round or ovoid in shape, reaching a size of 1, 3, 6 or more cm, and as a rule they are unique lesions that could be considered as a "clinical model" to evaluate plasticity and recovery.

In a series of recent publications on the biomechanical data of acute experimental injury to the spinal cord of cats, dropping a 20-g mass from a height of 20 cm, large deformations due to the impact force were observed using high-speed cinematography or were recorded by a displacement transducer.

More recently, the results of an experiment on the mechanical and neurological response of cat spinal cord under static loading (Tin-Kan Hung et al., 1982) showed that the characteristics of the stress-strain relationship of the spinal cord under static loading are quite different from those under an impact force. Macroscopically, the overall

deformation of the spinal cord appears to be about the same. The stress distribution in a deformed spinal cord and the microscopic deformation of the tissues appear to be less in the static situation than for the dynamic one.

Microscopically, the deformation and possibly the rupture of neurons of the spinal cord are expected to depend upon the stress distribution and therefore the types of the loading, dynamic or static.

As with all tumours in this region, the most important effects are related to: (a) the spinal cord compression, compromising and displacing neurons and axons; (b) the collapse of veins giving way to areas of oedema; and (c) insufficient blood irrigation that can lead to ischaemia due to collapse of arteries.

With cysticercosis the problem of the inflammatory reaction must be added, appearing mainly at the level of the arachnoid membrane and also around the vessels, increasing the complications mentioned above, particularly the ischaemic aspect and the strangulation that is provoked in the spinal cord once the arachnoid becomes thick.

This group contains many variants with different pathology and different localization, and the lesions may be single or multiple. The scale designed for neurological signs is not ideal for these lesions but has proved a helpful guide to the neurological manifestations in cases of spinal cord compression and, to some degree, it also permits evaluation of the efficacy of the surgical team. Of the different factors studied, some, such as age and sex, seem to have no significant influence on post-operative improvement. Other factors definitely influence the post-operative improvement: time of evolution of the lesion, location in the horizontal plane, size of the tumour, and extent of the surgical resection. On this basis, the benign spinal cord compression with the worst prognosis in the post-operative period is the one with a prolonged evolution, with the lesion located anterior to the spinal cord, of large size, and partially resected. The lesion with the best post-operative prognosis is the one with a short evolution, in the dorsal or cervical regions, behind the dentate ligament, of small size and totally resected.

Evoked potentials in spinal compression

Neurological examination is a method of assessing the function of the central nervous system irrespective of the presence or absence of anatomical alterations.

Neuroelectrical activity depends upon neuronal vitality for its realization, and also gives an assessment of function; it has the advantage of being more precise, it can be graphically recorded, and often it can be expressed numerically.

Recent studies of recovery in patients with spinal cord compression have made use of somatosensory evoked potentials, comparing the results in the pre-operative with the immediate post-operative stages, and days and weeks after the operation, analysing the changes and checking their correspondence with the clinical findings.

Sensory evoked potentials represent the response of the central nervous system to the application of a specific extrinsic stimulus, sufficient to cause depolarization of a peripheral sensory or mixed nerve.

Two kinds of neuroelectric potentials may contribute to the genesis of the scalp-recorded evoked potentials: (1) action potentials caused by neuronal depolarization, and/or (2) graded postsynaptic potentials that are subthreshold excitatory or inhibitory postsynaptic potentials, arising probably at the dendrite or dendrosomatic level. Both of these depend on ionic current flow across neuronal membrane.

Spinal cord compression may cause an anatomical lesion or a metabolic and functional disorder of certain somaesthetic pathways, which may abolish in the first case or may change in the second all evoked potential wave peaks that arise in tracts or nuclei distal to the lesion.

Factors influencing recovery

Two factors influence recovery which could be directly correlated with plasticity: (1) the duration of the compression, and (2) the velocity of the compression, a metastatic tumour being an example of a fast-growing tumour, and a neurofibroma being an example of a slow-growing tumour.

Two other factors influencing recovery cannot be directly correlated with plasticity: (1) the location of the

tumour with respect to the spinal cord, compressing and displacing the cord in different directions (tumours in the posterior or lateral part of the cord exert compression like a small static loading force as compared with those located in the front of the cord, because the space here is very narrow), and (2) the proximity of the compression to the spinal cord blood vessels that could produce ischaemia, with possible necrosis of the nervous tissue (where there is necrosis, no recovery can be expected).

Recent Advances in Facial Nerve Surgery

The facial nerve can be exposed in its entire length and reconstructed from its intracranial portion up to where it gives off its peripheral branches at the stylomastoid foramen. In tumour surgery (cerebello-pontine tumours, basal tumours, parotid gland tumours) an attempt should be made to preserve the facial nerve using microsurgical technique. In about 80-90% of cases the facial nerve can be preserved; in the rest, nerve reconstruction should be carried out at the same operation.

The technique of intracranial-intratemporal facial nerve grafting was introduced in 1975. In the cases operated so far which have been followed up for a sufficient length of time, satisfying to very good results have been achieved. This method can be used not only in tumour surgery but also in facial nerve injury following basal skull fracture, when an otolaryngological procedure has not produced satisfactory results.

4. REHABILITATION AND SOCIAL ASPECTS

Psychometric Clues to Recovery from Brain Injury

Stroke

In 1976 the National Institute of Neurological and Communicative Disorders and Stroke (Sahs & Hartman) issued a statement intended to represent state-of-the-art knowledge of factors determining recovery from stroke. These factors can be summarized. Patients who are younger, more intelligent, better motivated, and have more sympathetic families have a better prognosis than patients who are less favoured in these respects. Further, patients with ischaemic stroke recover faster and more completely than do patients with haemorrhagic disease. A better prognosis also attends relatively restricted lesions, especially of the non-dominant hemisphere. Also, severity of symptoms reduces the chances of recovery. Finally, therapy begun within the first two months leads to better recovery than does delayed therapy.

Aphasia

Studies of recovery from aphasia differ according to the population studied, the assessment techniques used, and methodology. Nevertheless, some general conclusions emerge: (1) comprehension improves more than expression (Kenin & Swisher, 1972; Lomas & Kertesz, 1978; Prins et al., 1978; Sarno & Levita, 1981); (2) Broca's aphasics exhibit greater and faster recovery than Wernicke's aphasics and than global aphasics (e.g., Kertesz & McCabe, 1977), possibly due in part to the fact that Wernicke's aphasics are found to be 7-11 years older than Broca's aphasics (Obler et al., 1978; Harasymiw & Halper, 1981); (3) the greatest improvement generally occurs in the first 2-3 months after stroke (Sarno & Levita, 1981); (4) global aphasics show the least recovery, but while they exhibit the aforementioned pattern of greater recovery in comprehension, unlike the other groups they show the most improvement at six months to a year after injury (Sarno & Levita, 1981).

With regard to the role of therapy in recovery, the fact that studies vary in their assessment techniques and therapies precludes a uniform conclusion. Many studies indicate that therapy has no effect (e.g., Kertesz & McCabe, 1977). Two recent studies examined recovery from aphasia in

the context of treatment: Kertesz & McCabe (1977) and Basso et al. (1979) classified their etiologically heterogenous patients (cerebrovascular accident, subarachnoid haemorrhage, and trauma) by using different classification systems, test-retest intervals and means of assessment. Kertesz & McCabe used the Western Aphasia Battery, a condensed form of the Boston Diagnostic Aphasia Examination. Basso et al. used their own language examination, which tested oral expression, auditory verbal comprehension, writing and reading. Nevertheless, these two studies agree on the following results: (1) Broca's aphasics had a better prognosis than Wernicke's aphasics, and globally aphasic patients had the poorest prognosis, and (2) a greater improvement in comprehension than in expression was seen for all patient groups. However, a significant overall effect of therapy on recovery was observed only by Basso et al. This difference in results can be attributed to the following factors: (1) Kertesz & McCabe's patients were on average 7.2 years older than those of Basso et al., and the latter's untreated group were an average of 3.1 years older than the treated group (older patients might be expected to exhibit a slower or a lesser degree of recovery), and (2) in the study by Basso et al., only patients undergoing well-defined therapy in the author's clinic for three sessions per week for five consecutive months were included in the treated group, while Kertesz & McCabe could only report the "widely differing techniques" employed in their patients' therapy. Therefore, Basso et al. may have obtained treatment effects by reason of the additive effects of having a younger patient population than Kertesz & McCabe, and having a better defined and more consistent therapy treatment.

Deficits associated with right hemisphere damage

Lesions of the right hemisphere often result in deficits in the ability to attend to and manipulate objects in extrapersonal and even personal space contralateral to the damaged right hemisphere. There is little evidence concerning the natural course of recovery from such deficits. Campbell & Oxbury (1976) studied patients after right hemisphere cerebrovascular accidents by giving them tasks of drawing symmetrical figures (clock, daisy), and various tasks believed to be sensitive to right hemisphere damage (WAIS block design, Stanford-Binet cube counting, Gollin incomplete figures, visual recognition (Warrington & James, 1967), and Raven standard progressive matrices). While only 2-6 patients still exhibited signs of neglect on figure drawing at six months post-stroke, all six patients

were significantly impaired on cube counting, block design, visual recognition and incomplete figures.

Closed head injury

Closed head injury is seen most often in young males who are socially maladjusted, e.g., with a history of petty crime, infrequent employment and alcoholism (Fahey et al., 1975), and this must be considered in formulating a control group. A sizeable proportion of such patients experience deficits in language as a consequence of injury. Sarno (1980) has reported that 32% of a sample of CHI patients tested 3-4 years after injury were obviously aphasic, but even those with no overt aphasia in spontaneous speech exhibited verbal impairment with formal testing. Thomsen (1975) also found deficits on follow-up testing three years after injury in patients who had recovered from their post-traumatic aphasia. Nearly all authors report that anomic aphasia is the most common type seen in closed head injury (Thomsen, 1975; Levin et al., 1976, 1980), occurring most often as a result of mild diffuse and focal left hemisphere brain damage.

In contrast to the general agreement on linguistic deficits following this kind of injury, there is no total consensus on the course of recovery of cognitive functions. Post-traumatic amnesia - a period of confusion, disorientation, and retrograde and anterograde amnesia after a head injury - has been viewed as an index of the severity of the injury, although the supporting evidence is not always consistent or convincing (see reviews by Smith, 1961; Schachter & Crovitz, 1977). Several recent studies have avoided some of the methodological and statistical problems of earlier reports. Using the WAIS as a measure of cognitive function, Mandleberg (1975, 1976) and Mandleberg & Brooks (1975) obtained serial WAIS scores from patients grouped by degree of severity of closed head injury, as measured by duration of post-traumatic amnesia, ranging from less than one week to over eight weeks. They found that verbal IQ recovered faster than performance IQ, severely injured patients eventually reaching average levels of ability. Moreover, Mandleberg (1976) determined that duration of post-traumatic amnesia ceased to be useful for predicting cognitive recovery by 3-6 months for verbal IQ and by 7-12 months for performance IQ. While there was a trend for the patients whose post-traumatic amnesia lasted longer to perform at lower levels, no significant differences were

seen by Mandleberg (1976) for the WAIS and by Brooks et al. (1980) for the Raven standard progressive matrices, the WAIS block design, the token test, or tests of vocabulary or paired associate learning. Only one study (Levin et al., 1979) reported WAIS IQs more than one standard deviation below normal at long-term follow-up. This study used duration of coma rather than duration of amnesia as an index of severity and used the Glasgow outcome scale to group the patients according to their adjustment to activities of daily living at follow-up. The "moderately disabled" and "severely disabled" patients obtained the subnormal IQ scores at greater than a year median follow-up. It should be noted that while the median interval was just over one year, the range was four months (for patients experiencing "good recovery") to 9 years (for "moderately disabled" patients), with "severely disabled" patients seen at a range of 9-30 months. Although the absence of reported means makes it difficult to be certain, it is possible that the "severely disabled" group was retested at intervals that were, on average, shorter relative to the other groups. If so, this would weaken the conclusion of significant long-term cognitive deficit for the "moderately" and "severely" disabled patients. However, Levin et al. were in agreement with Mandleberg and Brooks in finding that performance IQ predicted outcome better than did verbal IQ.

There is also literature addressing the issue of recovery of memory function after closed head injury. That some sort of memory retrieval exists during post-traumatic amnesia is indicated by Mandleberg's (1975) finding that patients tested during amnesia were able to attain a "borderline" score on the verbal section of the WAIS. The early literature on the recovery of memory function provides conflicting results, which have been reviewed by Schachter & Crovitz (1977). Brooks (1972, 1974) found no significant association between time since injury and memory performance, although, more recently, Brooks et al. (1980) observed a significant negative association between the duration of amnesia and immediate and delayed recall at two-year follow-up. Brooks investigated the recovery of short-term and long-term memory in patients grouped on the basis of time since injury (2.4 months and 16.6 months). While the groups did not differ on long-term memory, the patients 16.6 months post-trauma were significantly better on tests of short-term memory. Considering long-term follow-up, Smith (1974) has claimed memory deficits on the Weschler memory scale 10-20 years after injury. In contrast, Dencker (1960) compared the performance of monozygotic twins who had

experienced closed head injury ten years before testing with the performance of their non-injured twins and found no difference on tests of digit span and paragraph recall. More recently, Levin et al. (1979) evaluated memory recovery using the selective reminding technique of Buschke & Fuld (1974), in which the subject hears on 12 trials of 12 common words only those words he failed to recall on the preceding trial. All groups showed improvement across trials and increased retrieval from long-term storage, but these increases were significant only for the "good recovery" and "moderately disabled" groups and not for the "severely disabled" group. However, the concern previously expressed over this study's differential follow-up intervals for these groups suggest caution in interpreting these memory results as well.

Lezak (1976) also investigated verbal memory and learning by measuring WAIS digit span, Rey's auditory-verbal learning test and tests of immediate memory with varying degrees of overload, interference and delay. Over one-, two- and three-year follow-up testing, only immediate recall recovered significantly. This result is consistent with Dencker's finding of no deficits in tasks of essentially immediate recall at ten-year follow-up. While this literature is characterized by conflicting results, there is some hint of relative sparing of iconic and short-term memory. Unlike post-traumatic amnesia, age, side of lesion and presence of skull fracture were not found useful in predicting recovery.

Penetrating brain injury

Newcombe (1969) and Teuber (1975) have studied the late effects of missile wounds of the brain by following men with known brain injuries sustained during military service. The picture that emerges from these studies differs in important ways from that derived from studies of stroke and closed head injury. Specific deficits are remarkably unchanged over 20-30 years once an initial 2-3-year period of resolution passes. These deficits include visual field defects after occipital wounding, prosopagnosia after right posterior-sector penetration, and two-click discrimination after left temporal penetration. Lasting and severe deficits have been reported in perception of hidden figures by all penetrating brain wound patients (Teuber & Weinstein, 1956). More recently, Corkin (1979) has examined war veterans 20 years after wounding and found that size of lesion in left or right hemisphere is reflected in

performance on the hidden figures test. The nature of the deficit revealed by this test remains unclear, but its significance may lie in its dissociability from general intelligence.

Teuber (1975) also has reported that memory problems persisting 20 years after war injury were associated with both post-traumatic and retrograde amnesia. Evidence from some cases suggested that both intermediate (greater than one day to one week) and long (greater than one week) amnesia was associated with decreased intelligence and with impaired detection after left temporal penetration.

In marked contrast, Teuber has reported that intelligence suffers in comparison with pre-injury levels in only a third of men with penetrating missile wounds. A decline in intelligence after injury was most often seen with left parieto-temporal penetrations when cases of dysphasia were excluded. About two-thirds of this group are employed at or near pre-morbid capacity. A recent study of recovery from sequelae of penetrating head injury supports this finding (Mohr et al., 1980). Whereas hemiparesis stabilized by the end of the first year (after decreasing in the face but persisting in the hand), aphasia continued to evolve and in 34% of the cases "disappeared" within 10 years. "Sensorimotor" aphasia usually changed to "motor" (Broca's) aphasia. In turn, Broca's aphasia disappeared in 16 out of 29 cases. "Sensory" (Wernicke's) aphasia was observed here to be rare (9%) and to persist unchanged. It should be noted that the presence and degree of aphasic symptoms was based on clinical observation rather than formal testing.

Head trauma occurring early in life

Age at time of injury has a bearing on the extent and nature of recovery observed. Woods & Teuber (1978) reported that children under 8 years of age when injured showed no clinical aphasia at follow-up. More recent work suggests that such recovery may be more apparent than real. Dennis & Kohn (1975) have observed that patients with left hemidecortication for infantile hemiplegia during the first year of life are impaired at syntactic processing in spite of verbal and non-verbal intelligence, which does not differ from that observed in patients with right hemidecortication. Even patients in whom right hemisphere speech representation (confirmed with sodium amytal testing) developed after perinatal left hemisphere lesions were found to have impaired syntactic comprehension (Kohn, 1980).

Woods & Carey (1979) present evidence that shows deficits in language function in the presence of apparent clinical recovery from aphasia. Thus it appears that language development is abnormal in the absence of intact left hemisphere speech areas.

Neurorehabilitation

The rehabilitation of patients with neurological diseases has two aims: to diminish the somatic impairment caused by lesions of the nervous system in order to gain the utmost independence, and to diminish the psychological disturbances. Therefore, rehabilitation means the therapeutic reduction or compensation of the somatic or mental impairment. The somatic impairment is caused by local or multifocal lesions of the brain or by diffuse brain lesions. Similar concepts are to be applied to lesions of the spinal cord and the peripheral nerves. Correspondingly, mental disturbances are caused by local or diffuse brain lesions such as the frontal lobe syndromes or the diffuse organic syndrome.

Psychological disturbance appears very often as the reaction of the individual to organic damage. Psychiatric dysfunction can aggravate organic lesions and can even cause functional impairments. Primary somatic dysfunction can be fixed by psychogenic disturbances.

The basis of each kind of rehabilitation has to be an exact examination of the impaired functions of the central nervous system and its mental reaction and of the peripheral nervous system and its functional disabilities.

Various forms of damage to the nervous system

A brain lesion arising from a head injury, a disturbance of blood circulation or an inflammation can cause local, multifocal or diffuse damage.

Brain damage can have different degrees of severity. Slight brain damage leads to transitory functional disturbance, which disappears mostly after a short time and with early therapy, as in the case of concussion or transitory ischaemic attack. Moderate, severe and very severe brain lesions mostly lead to defective syndromes. After early therapy they require exact and strict rehabilitation.

The severity and prognosis of a brain lesion depends not only on the localization, intensity and the type of the primary lesion but also on secondary and tertiary sequelae (Gerstenbrand et al., 1979).

Pathogenetically primary lesions arising from brain injury can be classified as cortical contusions, brain lacerations, intra- and extracerebral bleeding, periventricular lesions, rupture of the corpus callosum, brain stem contusion and open brain wounds. Similar conditions are to be found in the spinal cord and peripheral nerves.

Secondary lesions of the brain appear as a consequence of the primary lesions and their immediate outcome in relation to vital functions such as respiration and blood circulation.

An augmentation of volume and of intracranial pressure finally leads to a lateral or downward displacement of the superior brain stem (tentorial herniation) or the inferior brain stem (foraminal herniation). Both lead to the acute midbrain and the bulbar brain syndrome (McNealy & Plum, 1962; Gerstenbrand & Lücking, 1970). The consequent disturbances of consciousness and of the motor system as well as vegetative imbalance give rise to an augmentation of the basic metabolism, due to the highly elevated release of noradrenalin (Hackl et al., 1978) as well as ventilation impairment leading to hypoxia and hypoxaemia and electrolyte disturbance. The patient may require treatment with beta-blocking agents, hypercalorization, and, in special cases, human growth hormone (Hackl et al., 1978).

Tertiary lesions of the nervous system mostly appear after very severe brain lesions, e.g., brain injury, hypoxia and intoxication, which lead to an acute midbrain or bulbar syndrome. Their main sequelae are diffuse lesions of the white matter as well as of the cortex, the spinal cord and the peripheral nerves. These pathological features are caused mainly by malnutrition, undernourishment, electrolyte imbalance, neuroendocrine impairment, superadded infection, and normotensive hydrocephalus.

Quaternary lesions include the so-called boxer's encephalopathy and the consequences of residual epilepsy.

With lesions of the spinal cord the situation is less complicated. Lesions of the spinal cord may be caused by

trauma, bleeding, inflammation, white or haemorrhagic infarction due to ischaemia, or a tumour. The symptomatology in the acute and subacute stages depends on the localization, intensity, and type of damage. Multifocal lesions are rare, except with multiple sclerosis.

Similarly, the symptomatology of the peripheral nervous system is correlated with the localization, intensity and type of damage. The structure of the peripheral nerves allows an exact diagnosis of the lesion.

Programmes of neurorehabilitation

Three main kinds of rehabilitation can be distinguished: actual, temporary, and palliative. Actual rehabilitation after a single lesion leading to immediate disability without any remarkable progress (e.g., after brain injury or brain infarction) aims at full recovery of somatic and mental impairment, with complete and lasting reintegration into family, social and occupational life. Temporary rehabilitation in chronic and progressive sickness or recurrent disablement (e.g., the parkinsonian syndrome, myopathies and multiple sclerosis) aims at temporary improvement. In palliative rehabilitation, the rapidly progressive course of a disease and the impairment of the patient (e.g., with a malignant tumour) can be alleviated by operative or medical therapy only for a very short time.

An individual programme of rehabilitation has to be planned after a precise assessment of the lesions. The type of rehabilitation is decided on the basis of the results of complete clinical assessment and psychological testing (Gerstenbrand, 1969; Rumpl et al., 1979). By means of psychological testing vigilance, intellectual abilities and special local brain functions (e.g., speech and motor performance) have to be evaluated (Quatember et al., 1961; Maly et al., 1979). Strict follow-up is necessary in order to evaluate the effect of the rehabilitation programme and to protect the patient from late sequelae of the basic lesions of the nervous system.

Course of neurorehabilitation

Rehabilitation is designed to conserve the residual abilities and compensate depleted functions, as well as improve impaired functions. Logotherapy, ergotherapy and physical therapy have to be initiated correctly in order to achieve the most favourable result.

The programme of rehabilitation for a patient with a brain lesion can be divided into a preparatory phase, a phase of first communication, an activation phase, a mobilization phase, a stabilization phase, an integration phase, a resocialization phase, and a phase of after-care (Gerstenbrand, 1969). The duration of each phase depends on the condition and progress of the patient.

The organization of rehabilitation for severe and very severe cases can best be achieved within a therapeutic community (Gerstenbrand & Lücking, 1977). In rehabilitation centres, groups are formed in order to overcome the various social or psychological disturbances.

Patients with spinal cord lesions have to be treated and rehabilitated differently from those with lesions of the brain. Most important is motor training and training of the urinary bladder and the rectum. Additionally, psychological care is provided to support the patient in overcoming his disabilities.

The purpose of every rehabilitation programme is the reintegration of the patient into family, occupational and social life.

5. GUIDELINES FOR THE FUTURE

It is evident that recent scientific developments in the understanding of neuroplasticity have important implications for the diagnosis and treatment of disorders of the central nervous system in man. The prompt exchange of basic and clinical information between scientists and physicians is particularly important in view of the high and increasing incidence of head trauma in developing countries and its continued importance throughout the world.

Basic Studies

It is obvious that the neurons of the mammalian central nervous system have a marked capacity for regeneration. The main practical goal must now be to harness this capacity for the purpose of achieving functional recovery. First it will be important to establish the degree of functional connectivity that may accompany anatomical regrowth. This objective may be accomplished by means of quantitative neuroanatomical, electrophysiological, pharmacological and behavioural studies. Secondly, there is a need to determine the molecular basis of growth and connectivity. Studies are required to define the intrinsic mechanisms underlying neuronal repair and the extrinsic factors which influence them, such as neural factors (both stimulatory and inhibitory), surface constituents of neurons and glia, and other components of the neuronal environment, including target tissues. Of special importance is the biochemical characterization of various types of neuronotrophic and neurite-promoting factors in the mammalian central nervous system. Such characterization could well open up new possibilities for the medical treatment of injuries to the central nervous system in man.

The rapid development of neuroscientific studies in the field of neuroplasticity is likely to lead to the better management of brain and spinal cord lesions in man. The development of relevant experimental strategies will be highly dependent on the contribution of clinical studies in man. Nevertheless, current knowledge does not justify the application of neural grafting technologies to problems of human brain disorders.

Input from clinical experience and a continuing dialogue between the laboratory and the clinics is an essential component that should be immediately implemented and should be continued. The information derived from studies on

central neuroplasticity could well have a profound impact on the understanding of pathological conditions that affect the nervous system, their management and the design of new pharmacological approaches.

Two important aspects that need to be explored are: (1) the diagnosis and management of cranio-spinal trauma and its various facets of specific relevance to particular geographical areas of the world; and (2) the role of environmental factors (e.g., nutrition, toxins, and infectious disorders) in limiting the capacity for repair of the human nervous system.

Clinical and Related Studies

Revascularization surgery

Two major issues are important with respect to the surgical treatment of strokes. First, new methods need to be developed for the functional evaluation of patients before and after surgery. Studies in this area should include consideration of the natural history of cerebrovascular accidents in the absence of surgical intervention. Second, further studies should be undertaken to determine the functional capacity of the new vascular channels after anastomoses have developed or after collateral revascularization has been stimulated.

Hydrocephalus

Clinical, electrophysiologial and metabolic studies are required with specific focus on the reasons for the improvement noted after surgical treatment of hydrocephalus. Non-invasive methods (such as isotopic imaging) are recommended for such investigations. To complement these clinical studies, animal models of hydrocephalus (e.g., reovirus and mink encephalopathy) should be employed to study the effects of the enlarged ventricles on the brain by histological, metabolic and functional criteria. New pharmacological approaches should be sought in order to alleviate this condition.

Chronic spinal cord and brain compression

These clinical states also provide good clinical models for experimental studies of neuroplasticity. The experimental methods to be considered for these studies should include: quantitative immunohistochemical techniques,

metabolic studies, computed tomography, radiotracer techniques (positron and single photon emission tomography), nuclear magnetic resonance, and blood flow measurements. These studies are needed in order to select simpler techniques for treatment and to identify prognostic indicators for the total management of these disorders.

Rehabilitation

One of the prerequisites for the successful rehabilitation of patients with moderately severe brain injury is adequate management of the disease during its primary and secondary stages. Methods should be sought for the adequate diagnosis and treatment of head injuries in various parts of the world.

Training

Successful primary health care requires both doctors and paramedical staff. Their training should continue simultaneously, and should form part of a pyramid of health care delivery specifically devoted to the problems of head trauma. Training programmes will have to be developed in primary diagnosis, triage, and acute treatment of head injury, with specific reference to needs in various parts of the world. Emphasis must be given to the reduction of automobile accidents, which are the leading cause of these injuries.

If studies are carried out in the directions outlined above, there is no doubt that health care can be improved at the primary and other levels, in developed and developing countries alike.

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