

## Disorders of the brain: costs, recent progress and future possibilities

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As part of the Decade of the Brain in the United States, recent progress, future possibilities and costs of major disorders of the brain have been estimated. Numbers given in the following text are, in most cases, translated from this American status report (The National Advisory Neurological Disorder and Stroke Council, 1992). The US figures cannot be directly transferred to Europe, but undoubtedly have the right order of magnitude. Unfortunately, similar figures are not easily established for Europe, but where good European data have been available they have been cited. Figures for prevalences have partly been taken from original work, partly from a Danish document published by the Danish Ministry of Health (Sundhedsstyrelsen og HjerneÅret, 1996). The present paper is not a thorough review of all available evidence, but aims to give a popular overview which may provide useful arguments for 'Year of the Brain' initiatives and for promotion of our speciality in general.

In the Western world, more people are being admitted to hospital because of diseases in the brain than diseases in any other organ. The expense caused by disorders of the brain equal those for cardiovascular diseases and cancer combined. In the USA, the National Foundation for Brain Research has estimated direct and indirect annual costs for disorders of the brain, with particular emphasis on psychiatric diseases (The National Foundation for Brain Research, 1992). According to these (admittedly uncertain) estimates, neurological/psychiatric disorders cost more than 400 billion dollars, corresponding roughly to 500 billion ECU in Europe. The indirect costs, i.e. loss of work days, pensions etc., are much greater than the direct expenses, i.e. medical services, medicine and other treatments. This, of course, is due to the fact that most disorders of the brain are chronic and disabling, but not

lethal, at least not until after many years of the disease. Numbers from the American document are shown in Table 1. The total costs are calculated to be 7.3% of the gross national product in the US. Epidemiological data concerning the prevalence of some disorders of the brain in Europe, together with selected references, are shown in Table 2. In a joint effort, The World Health Organization, Harvard University and The World Bank recently estimated that disorders of the brain consume 25% of the total health costs (Murray and Lopez, 1996, 1997). The investment in prevention, diagnosis, treatment and rehabilitation of disorders of the brain is minimal, and totally out of proportion to the enormous costs inflicted upon society by these disorders. An increased expenditure within this area would, therefore, be a good investment in strict financial terms. The possible savings in terms of human suffering go beyond our imagination.

### Genetically determined diseases

Out of approximately 100 000 human genes, 60 000 are concerned with the development of the brain. It is not a surprise, therefore, that there are more than 500 disorders of the brain inherited in a Mendelian fashion. A large number of the responsible genes are already cloned and mutations have been identified. The future tasks in this area will be to identify the remaining genes and all mutations involved, to explore the

TABLE 1. Cost of disorders of the brain (USA) (3)

Neurological disorders:	104 000 mill \$
Psychiatric disorders:	136 000 mill \$
Alcohol abuse:	90 000 mill \$
Drug abuse:	71 000 mill \$
Total:	401 000 mill \$

TABLE 2. Prevalence of selected disorders of the nervous system in European countries (EU, EFTA, COST)

Disorder	Country	Author	Prevalence (cases/10 000)
Dementia	Federal Republic of Germany	Cooper <i>et al.</i> , 1989	6 400
	Italy	Rocca <i>et al.</i> , 1990	8 400
	The Netherlands	Breteler <i>et al.</i> , 1992	6 900
	Sweden	Rorsman 1986	6 400
Cerebrovascular disorders	Greece	Paschalis 1989	990
	Finland	Aho <i>et al.</i> , 1986	820
Migraine	Denmark	Rasmussen 1996	10 500
	Italy	D'Alessandro <i>et al.</i> , 1988	13 500
	France	Henry <i>et al.</i> , 1992	12 000
Chronic Tension-type headache	Denmark	Rasmussen 1996	3 000
Epilepsy	Finland	Keranen <i>et al.</i> , 1988	630
	Italy	Granieri <i>et al.</i> , 1983	620
	United Kingdom	Goodridge and Shorvon, 1983	500

functions of these genes in their normal and mutated form, and to increase our understanding of gene/environment interactions. This will lead to unheard of progress in our understanding of the mechanisms of diseases of the brain, and of the understanding of normal brain functioning. Such insight will enable the development of novel pharmacotherapy on a much more rational basis, but it will also lead to better possibilities for prophylaxis. For the more disabling or lethal disorders, gene therapy will probably become available.

#### Developmental neurology

Developmental neurological disorders are attributable to brain damage acquired early in life. Some disorders have a genetic basis and thus overlap with the genetically determined diseases. The developmental disorders include cerebral palsy, spina bifida, 'minimal brain dysfunction', dyslexia, and different forms of mental retardation. Approximately 10% of the population are affected to some extent. Most suffer from a minor dysfunction, but approximately 2% have a severe developmental disorder. The disorders cost 100 million ECU per 1 million inhabitants each year, and the problem is increasing, probably because of an increase in premature births. Prevention will be the key to success in this area, but novel treatment possibilities are underway. General principles developed within neurological and neuropsychological rehabilitation should also be applied to this group of patients.

#### Epilepsy

The lifetime prevalence of epilepsy is almost 1%, and socio-economic costs are 20 million ECU per 1 million inhabitants per year. The discovery of the genetic basis of some forms of epilepsy is well underway and will prove immensely useful. Different genes are likely to

code for receptors, ion channels or enzymes, reflecting the basic mechanisms of epilepsy. There are several excellent animal models of epilepsy. Novel drugs will have more specific action and fewer side effects than currently used anti-epileptic compounds.

#### Traumatic damage of the brain and spinal cord

Five hundred people out of a million annually contract traumatic brain damage, out of these 20% have severe brain injury. The socio-economic costs total approximately 60 million ECU per 1 million inhabitants each year. Not all the damage occurs immediately after the trauma. Significant secondary brain damage takes place over a prolonged period of time and may be prevented by improved management, pharmacological interventions are presently being evaluated. For spinal cord damage, neurotrophic factors are being explored with or without transplantation of foetal neurons. These extremely interesting novel principles must not overshadow the fact that early intensive and multidisciplinary treatment and rehabilitation with existing means are rewarding, and should be available throughout Europe in dedicated trauma centres.

#### Stroke

Approximately 2000 out of a million people each year suffer a stroke, which is the third most frequent cause of death. Among the survivors, severe motor and/or mental disability is common. The socio-economic costs are 80 million ECU per 1 million inhabitants each year. All stroke patients should be immediately admitted to special units, where vital functions can be monitored and progression closely observed. Stroke units also facilitate the use of thrombolysis and the testing of novel drugs and other treatments. Worldwide, a large number of compounds which have proven effective in animal experimental stroke models are

under development. Early intensive multidisciplinary rehabilitation is best given in a dedicated stroke unit associated with a neurological department.

#### Brain tumours

There are approximately 150 cases of brain tumours per million inhabitants each year in Europe, half of these are primary and half are secondary tumours. Work is ongoing to develop better treatments, including sensitive monoclonal antibodies, gene therapy, targeted uptake of radionuclides, and better chemotherapy. Novel neurosurgical techniques, such as the gamma knife, continue to be refined. Despite this progress, the possibility of a cure for brain tumours is not yet within reach.

#### Dementia

The prevalence of dementia of a medium to severe degree is 10 000 per million. Diseases with dementia annually cost 250 million ECU per million inhabitants; dementia is the cause of 60% of all nursing home placements. Various estimates have indicated that up to 15% of people placed in a nursing home under the diagnosis of dementia actually suffer from something else, and that 2/3 of these people can be treated. This group of patients, therefore, should be diagnosed by a neurologist and, when needed, by a psychiatrist. Neuropsychological assessment is often required. After proper diagnosis, patients with Alzheimer's dementia may now be offered one of the recently marketed drugs with proven, although modest, symptomatic efficacy. Patients with vascular dementia should have secondary prophylaxis. The discovery of part of the genetic basis of Alzheimer's disease has made possible the creation of models using transgenic mice. The search for novel drugs is now focussed not only on symptomatic treatment, but also on treatments which may slow or prevent amyloid formation and the associated degeneration. Furthermore, neuroprotective compounds, growth factors and drugs acting against nitric oxide are being tested.

#### Multiple sclerosis (MS)

This disease affects 1000 people per million in Northern Europe and costs 30 million ECU per 1 million inhabitants (Jönsson, 1995). The importance of auto reactive T-lymphocytes is increasingly acknowledged. The introduction of  $\beta$ -interferon as the first compound with a proven, albeit modest effect on the development of the disease, has created excitement and enthusiasm. Soon, several  $\beta$ -interferons will be on the market, and copolymer 1 too. The animal model experimental allergic encephalomyelitis appears to have a predictive value for therapeutic efficacy in multiple sclerosis,

since both  $\beta$ -interferon and copolymer 1 are effective in this model. A number of other compounds are under preclinical and clinical trial. Furthermore,  $\beta$ -interferon and copolymer 1 are under investigation for their efficacy in primary and secondary progressive MS. It seems likely that within a few years all MS patients will be on one treatment or the other and will require regular control at a neurological department.

#### Neuromuscular diseases

This heterogeneous group of diseases which includes many relatively rare conditions affects 2000 per 1 million inhabitants. Among the most common are the carpal tunnel syndrome, ulnar and peroneal nerve palsy, and the various polyneuropathies. More rare, but of high impact on the individual, are the muscular dystrophies, amyotrophic lateral sclerosis and myasthenia gravis. Most of the genes and mutations causing muscular dystrophies and inherited neuropathies are known. The Guillain-Barré syndrome can be treated with intravenous immunoglobulin or plasmapheresis, and other treatments are likely to appear.

#### Neuroinfections

Viral meningitis, bacterial meningitis and encephalitis are well-known neuroinfections. During the 1980s, four additional neuroinfections have been recognized. These are: neuroborreliosis caused by a spirochaete, the prion diseases caused by an abnormal structural protein, tropical spastic paraparesis caused by the HTLV-1 virus, and neuro-AIDS caused by the HIV virus. It is not generally appreciated that more than one in three AIDS patients suffer symptoms from the central and/or the peripheral nerve system. If a treatment for AIDS ever becomes possible, the major obstacle will probably be to eradicate the disease in the brain, because of its protection by the blood-brain barrier.

#### Movement disorders

Parkinson's disease affects 1000 people per million. New drugs against Parkinson's disease include synthetic dopamine agonists, dopamine re-uptake inhibitors and catechol-*o*-methyltransferase inhibitors. Work is increasingly focussing on the possibility of using neuroprotective drugs, or other drugs which can slow disease progression, but is so far without success. The introduction of botulinum toxin for dystonia has been a revolution and new indications for such treatment continue to be developed. For example, the toxin is highly useful against spasticity when used as part of a more comprehensive neurorehabilitation programme including physiotherapy.

### Substance abuse

Many abused substances can cause serious brain damage. Examples of this are strokes in cocaine and crack users, alcohol-induced damage of the central and peripheral nervous systems, brain damage caused by prenatal exposure to neurotropic substances, and secondary damage due to AIDS from intravenous drug abuse. The total socio-economic costs of abuse are probably around 250 million ECU per 1 million inhabitants. New neurobiological research results have demonstrated the importance of the dopaminergic reward system in the brain stem and have increased the understanding of receptor mechanisms leading to tolerance and increased drug need. Genetic studies indicate a genetic factor in some alcoholics.

### Pain and headache

Chronic pain cannot be explained by peripheral mechanisms activating peripheral nociceptors alone. Chronic pain sensitizes the central nervous system because of a number of secondary neuronal changes. In the dorsal horn of the spinal cord these mechanisms have been elucidated at the level of receptors, second messengers and gene expression. The huge advances in the understanding of basic pain mechanisms are expected to result soon in the development of a more rational pharmacotherapy of pain. Perhaps the more than 100-year-old drug of choice, acetylsalicylic acid, can find its successor within the next decade. Among the painful neurological syndromes, migraine and chronic headache of the tension-type are the most important. Headache diseases annually cost 70 million ECU per 1 million inhabitants (Rasmussen, 1996). In the general population at least 50 000 people per million at any given time are severely affected. The rare familial hemiplegic migraine has been shown to be caused by mutations in a gene coding for a calcium channel subunit, and linkage has recently been found at two other sites. The search for the genes of the common type, migraine with aura and migraine without aura, has now begun. In addition, the pathophysiological understanding of migraine makes rapid progress. Nitric oxide, and probably the calcitonin gene-related peptide, is a key molecule. Cortical spreading depression seems to be the underlying cause of the aura. The development of a host of drugs is now underway. These include novel 5HT<sub>1D</sub> receptor agonists and other drugs that target CGRP receptors, nitric oxide formation and cortical spreading depression.

### Schizophrenia

Approximately 3000 people per million suffer from schizophrenia, and many more from schizophreniform disorders of different severity. Direct and indirect costs

of these severely invalidating disorders are approximately 150 million ECU per 1 million inhabitants. The biological basis of the disease is now being intensely investigated. Structural changes in the brains of the affected have been demonstrated and are thought to relate to developmental disturbances. A lack of activation of the frontal lobes on functional neuroimaging, differences in MR-appearance, and a considerably decreased number of thalamic interneurons, are among the neurobiological abnormalities demonstrated in schizophrenia. Drug treatment is in progress, but it is increasingly appreciated that interaction with the environment, psychological and social support, and different educational measures, are and will remain equally important.

### Manic-depressive illness

Distinction is made between the bipolar type where mania and depression alternate, and the unipolar form with depressions only. The bipolar type affects 1% of the population. Lithium prophylaxis has proven efficacy. Anti-epileptic drugs are now also increasingly being used. The unipolar disorder affects at any given time 2–3% of the population, and usually responds well to modern antidepressive drugs. The costs of major depression are 200 million ECU per 1 million inhabitants. The genetic basis of the disorder is being intensively investigated but is not yet clarified. In most cases, gene-environment interaction is necessary in order to create an episode of depression. It has been estimated that available treatments can help 80% of those affected, a spectacular success which few other fields of medicine can match.

### Some front lines in neuropsychology

Neuropsychology aims at elucidating the relationship between psychological and neural processes. In an international perspective, neuropsychology today is one of the fastest growing branches of psychology. The subspecialty stands upon a solid basis of experimental psychology, psychometrics and developmental (lifespan) psychology. Neuropsychology focuses on many of the most important functions of the brain: perception, learning, memory, language, problem solving, emotions and patterns of action. Neuropsychological research is currently extremely active. It is often interdisciplinary, linking basic and clinical sciences, and it uses increasingly sophisticated experimental techniques, test batteries and animal models. Using functional imaging, such as SPECT, PET and functional MR, it has become possible to look into the living brain and map psychological functions which previously could only be studied indirectly.

The last two decades of research have challenged

many conventional ideas about the brain. The nervous system has proven much more plastic than experts once believed. A well-learned skill activates the brain in a different way from a novel task. A violin virtuoso who expresses himself with the fingers of the left hand has a larger cortical representation of the left hand than other musicians. Unexpected differences have also been shown between the two sexes. Thus, adult women in the northern hemisphere seem to use both halves of the brain in language tasks, whereas males predominantly use the left hemisphere. Well-established functions of various parts of the central nervous system have been challenged. The cerebellum, for instance, was previously regarded as a centre for motor coordination. Animal experimental studies, as well as human brain imaging studies, have shown that the cerebellum plays an important role in basic learning and memory.

Most diseases of the brain affect its psychological functioning, but the type and degree of impairment depend upon the type of disease, its localization and extent. In diseases like Parkinsonism and multiple sclerosis, intellectual dysfunctions are important, although not immediately obvious. Patients and their relatives often appreciate the possibility to have neuropsychological impairments examined and described. Neuropsychological counselling and training can play a valuable role for increasing insight and tolerance, and for acquisition of compensation strategies.

#### The future of brain research in Europe

Brain research, as previously discussed, has been given some priority by the EU. In many countries the national research council has pronounced brain research a prioritized area. Much more needs to be done, however. We need an EU initiative which can parallel the American Decade of the Brain and the huge investments that the Japanese have recently made in brain research. Several attempts have been made but so far with little success, perhaps because they have been led by basic scientists. An *ad hoc* committee of experts from the so-called COST countries has produced the report 'Neuroscience research in Europe'. A total of 12 areas were identified which deserve increased effort: developmental neurobiology, molecular neurobiology, sensory processing, control of movement, autonomic nervous system, neuroendocrinology and neuroimmunology, cognitive neurobiology, learning and memory, mental diseases, ageing processes, degenerative diseases, CNS injury and repair. Recently, a group under the Commission of the EU, headed by Professor Jean-Pierre Changeux from Paris, has prepared a report entitled 'The Neurosciences at the Services of European Society'. This report focuses on the possibility of creating a multidisciplinary brain research programme

separate from the Biomed programme. It points out that brain research has enormous implications for many areas other than health. The considerations about these issues are shown in Table 3. The committee recommends in addition four major areas of increased effort, as mentioned in Table 4. The specific recommendations are firstly to create a multidisciplinary research programme, as part of the fifth framework programme for research and development. Increased financial support should be given to the main areas described in the report. Ph.D. educations and post-doctoral training in basal and clinical neuroscience should be supported by the creation of a common European Ph.D. degree, by increasing the number of exchange scholarships and organizing technical workshops, courses in laboratory techniques, and schools for basic neuroscience. It has been suggested that the interaction between basic and clinical neuroscience should be increased, and that European laboratories of excellence in the neurosciences should be established, which should make available new and extremely costly technology for scientists all over Europe. European databases concerning the human brain and the brains of a number of experimental animals should be created. These databases should

TABLE 3. Vigorous support for Neurosciences is important to Europe for four major reasons

Basic Research:	Knowing how the brain works is the only way to understand ourselves, how we perceive external events, how we think, how we feel, and how we remember.
Medicine:	The effects of aging, drug addiction, pain, neurological and psychiatric diseases are enormously damaging to our society. Up to 30% of medical expenses in Europe concern the nervous system.
Society:	Education, language learning, social behaviour and care of behavioural disorders will all benefit directly from our understanding of brain function.
Industry:	Neuroscience discoveries are directly transferable to European biotechnology, pharmaceutical and information industries and will permit optimal design of new generations of 'intelligent' computers and robotic devices.

TABLE 4. Areas which are particularly worthy of increased support

A.	Brain theories, computer neuroscience and neuroinformatics
B.	The development of the brain, brain diseases and brain recovery
C.	Intracellular communication in the normal and pathological brain and mechanisms for learning and memory
D.	Human behaviour and functional brain mapping.

contain anatomical, molecular, biochemical and physiological behavioural data, and other data. Better procedures need to be established for the evaluation of scientists, laboratories and research programmes at the European level. Neuroscientific meetings in Europe should be supported, as should federations of national neuroscientific societies and neuroscientific journals. Finally, the relationship between European neuroscience and the pharmaceutical industry should be strengthened by joint workshops, joint research programme funding, and by increasing the exchange of scientists between pharmaceutical industry and universities.

The programme has not been accepted, however, and resources for brain research are unlikely to be increased in the fourth framework programme. It seems necessary that European neurologists take the lead in future efforts to create a European decade of the brain.

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