

EUROBRAIN

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It's Euro Time! After the Euro, the new currency of the European community, it's now time for *EuroBrain*, a newsletter published by the European Dana Alliance for the Brain (EDAB).

EDAB is a non-profit organisation devoted to raise the public profile of brain research. It was launched in 1997 by the Charles A. Dana Foundation, a private, philanthropic foundation, headquartered in New York, USA, with grant programs in health and education, who also funded EDAB's sister organisation, the Dana Alliance for Brain Initiatives in the United States. EDAB brings what is being accomplished in scientific laboratories to the general public and policy makers. EDAB's mission is to make vital information accessible and understandable to all.

EuroBrain will bring regular updates on the most recent advances in neuroscience particularly as they relate to the understanding and hopefully cure of diseases of

the nervous system. *EuroBrain* is intended for the non-specialist.

Each edition of *EuroBrain* will include an overview of a particular subject, a focus on some "hot" new developments, a contribution by a leading European neuroscientist as well as a "personal note" by someone sharing his/her experience with a disease, or by an advocacy group.

The first issue is devoted to depression, a condition that affects several million Europeans.

It is the hope of EDAB that *EuroBrain* will provide a useful source of information about neuroscience and contribute to bringing scientists and clinicians closer to the public.

Pierre J. Magistretti, Professor of Physiology,
Institute of Physiology,
University of Lausanne, Switzerland

Colin Blakemore, Waynflete Professor of Physiology,
University Laboratory of Physiology, Oxford, UK



**The European
Dana Alliance
for the Brain**

CONTACT

Béatrice Roth, B.
Institut de Physiologie
7, rue du Bugnon
CH-1005 Lausanne
Switzerland
Tel./Fax: +41 21 692 55 25
dana1997@iphysiolsg1.unil.ch

Elaine Snell
Vicarage House
58-60 Kensington Church Street
London W8 4DB, UK
Tel.: +44 171 937 7713
Fax: +44 171 937 4314
edab@which.net

Depression

*THE BLACK DOG HOVERS
IN THE CORNER,
GROWLING QUIETLY,
MENACING,
ALWAYS THREATENING.*

Black dog

The black dog hovers in the corner, growling quietly, menacing, always threatening. Sir Winston Churchill described his depression as “the black dog”, a sinister companion with the unpredictable ability to dominate normal daily life. There is a cruel irony in the word itself. People say they are depressed when they are having a less than good day but, in its correct interpretation, depression is a severe illness that affects one in 10 people, wherever they are in the world. It can happen to anyone at any age. It is debilitating, it is serious but it is treatable. Yet there is a stigma attached to depression.

Make no mistake – depression is an illness.

But what exactly is depression? Even sufferers of depression find it difficult to express, but essentially it is an overwhelming feeling of sadness, a loss of interest in life, a feeling of worthlessness and low self-esteem – and, sometimes, a desire to die. Manic depression is different. People with manic depression experience a roller-

coaster of elation and suicidal feelings with relatively stable periods in between. Depression manifests itself at work and home, so it is not just the afflicted person who is affected. It is very, very difficult to live or work with a depressed person. Despite their care and love, family and friends can only play a supportive role. The patient needs psychiatric and medical help. There is no precise diagnosis: you cannot have a blood test for depression. Psychiatrists, however, have defined a set of criteria and a combination of any five constitute depression.

The symptoms include:

- prolonged sadness or unexplained crying spells
- anxiety, irritability, anger
- diminished interest in life
- significant weight loss or weight gain
- reduced control over body movements; unexplained aches and pains
- fatigue and lethargy
- feelings of worthlessness
- inability to think and concentrate
- recurring thoughts of suicide or death.

TREATING DEPRESSION

Prozac and other anti-depressants work well but act slowly leaving the patient in a depressed state for up to four weeks while the drug takes effect. The patient, understandably, may assume the medication is not doing any good and may simply give up the course of treatment or, worse still, their risk of suicide will increase. Current therapy also can cause side-effects such as dizziness, constipation or drowsiness and reduced libido.

Emotional “P”ain

There is now considerable excitement over a promising new therapy based on a naturally occurring chemical called “Substance P”. “P” stands for pain and the substance is responsible for sending messages about pain from the skin to the brain. It also plays a part in emotion. In experiments, administration of Substance P caused anxiety and depression. Researchers have found that the actions of Substance P that cause depression can be blocked by a newly developed molecule improving patients’ symptoms (M. S. Kramer, et al., *Science*, 1998, Vol. 281, p. 1640-1645). Moreover, there seem to be significantly fewer unpleasant side-effects compared with some of the drugs currently available. Although the drug is still in its trial phases, doctors and scientists are very optimistic. This Substance P blocker seems to be the first new neuro-chemical system for depression to appear in 50 years.

Perhaps it is of some comfort to those who wonder why they cannot “snap out of it” that research in recent years has yielded some striking physical and genetic components closely linked to depression.

The biology of depression

Powerful technology (MRI and PET scans), enables brain researchers to see images of the brain and areas of activity. In depressed people the imaging techniques show that the activity of those parts of the brain, that govern emotions is actually altered. A downward spiral of sadness leads to automatic negative thoughts that provokes structural changes in the brain causing further sadness, and so forth. This spiral is accompanied by shifting levels of chemicals that affect the brain, such as the stress hormone, cortisol. The delicate balance of an array of brain’s chemical messengers, called neurotransmitters, that are normally regulated to cope with the demands of daily life, is disturbed in depressed people.

There is not a “depression gene” but it is now certain that several genes will prove to be involved in conferring a predisposition to depression. Their function in this respect may lie dormant indefinitely but a distressing event, such as the death in the family, can then kick these genes into action and the result will develop into depression. Thus, it is not the distressing event that causes depression, but it acts as a trigger. The question, therefore, is “why do some people get depressed as a result of a traumatic experience, when other people are apparently better able to cope?” Further genetic and psychiatric research will help to identify those who are most vulnerable which is an important goal for this costly illness.

The stigma of depression

It is immensely difficult to overcome the hurdle of the stigma attached to depression. Buckling under pressure is seen as a weakness that would be a hindrance, say, in business where time is money and absenteeism is costly. Even amongst family and friends, depression is an uncomfortable thing to admit to, so better left unsaid. Overcoming this stigma is crucial. There is more to an increasingly long life than the number of years. Depression, as well as dementia, pose a major threat to the quality of longevity. At the other end of the age spectrum, as many as 15 percent of teenagers are thought to suffer from depression. This cannot be dismissed as just teenage moods when 2 to 3 percent of teenage girls alone attempt suicide. Even more insidious is that children who become depressed are getting younger.

All in the mind ?

Last year, the European Dana Alliance for the Brain commissioned a major survey on attitudes to brain-related disorders. The survey examined people’s perceptions of a wide range of illnesses such as

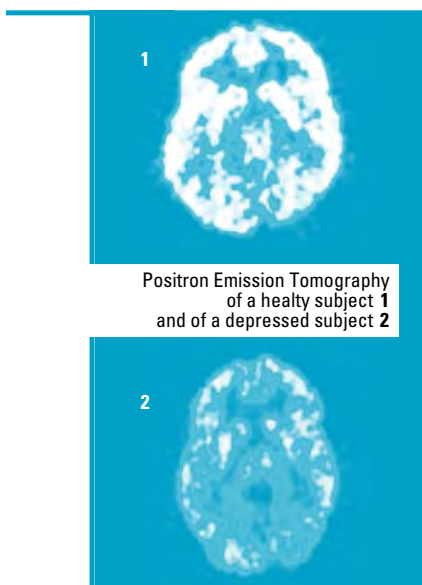
Parkinson’s and Alzheimer’s diseases, stroke, schizophrenia, depression, eating disorders and spinal injury. One of the most striking features was that the public fails to link the brain with depression.

Along with conditions like anorexia and bulimia nervosa, depression is widely regarded to be all in the mind and self-inflicted, but not considered to be a brain disorder. By contrast, the majority of people regarded diseases like Alzheimer’s, Parkinson’s and Creutzfeldt-Jakob – or CJD – (the human form of “mad cow” disease) clearly as disorders of the brain.

The cost of depression

As stated, depression affects one in 10 people world-wide irrespective of differing cultures. In the UK, anxiety and depression contribute mainly to more than 90 million working days lost due to mental health problems, costing the country £22 billion a year but the burden on the patient’s family and carers is incalculable. The World Health Organisation predicts that the loss of healthy life caused by major depression will increase by more than 50% by the year 2020 to 78 million person/years of lost healthy life every year world-wide.

This is a brief attempt to describe the scale of the problem of depression in human and economic terms. There is an urgent need for patients to be more accurately diagnosed and to be treated effectively. Throughout Europe, neuroscientists and geneticists, together with psychologists and psychiatrists, are beginning to unravel the complexities of the brain and how it manages emotion and thought, action and deed. Scientific understanding of how the mind processes thoughts provide clues for new treatment. Tolerance of this devastating illness will remove the mask of pretence that so many people feel they have to hide behind.



Positron Emission Tomography of a healthy subject 1 and of a depressed subject 2



Professor Lewis Wolpert

A personal view of depression

It was the worst experience in my life. I was in a state that bears no resemblance to anything I had experienced before. It was not just feeling very low, depressed in the commonly used sense of the word. I was seriously ill. I was totally self-involved, negative and thought about suicide most of the time. I could not think properly let alone work and wanted to remain curled up in bed all day. I had panic attacks if left alone. And there were numerous physical symptoms – my whole skin would seem to be on fire and there were uncontrollable twitches. Every new physical sign caused extreme anxiety. I was terrified, for example that I would be unable to urinate. Sleep was impossible without sleeping pills which only worked for a few hours and when I woke up I felt worse. The future was hopeless. I was convinced that I would never work again or recover. There was the strong fear that I might go mad. I had never been seriously depressed before. On previous occasions the way I

dealt with mild depressions – feeling low – was to go jogging. I have to admit that I rather sneeringly proclaimed that I believed in the Sock School of Psychiatry – just pull them up when feeling low. But that certainly does not work with serious depression.

I was admitted to the psychiatric ward of the local hospital. I was taken out every morning by one of my family and returned around five each evening. Being in hospital was both shocking and comforting. However, after several tortuous weeks I began slowly to improve. I could leave the hospital on my own and go for walks. There were bad days and better days and of great relevance I could tell the difference.

Being at home put a great strain on my wife for I found it very difficult being left on my own in the flat for even quite short periods even a few hours. The following day I started cognitive therapy as an outpatient and this was tremendously helpful. My therapist introduced me to a new set of

relaxation techniques which she suggested I do each time anxiety or panic attacks started. She reassured me that I would not go mad.

Cognitive therapy may sometimes sound like little more than common sense, but I really needed it and it helped. As I slowly improved, I contemplated going to my first committee meeting since falling ill. What my therapist helped me envisage were the likely negative possibilities; how bad would it be, for example, if I went and then had to leave. Would my colleagues be very critical? I decided to go. Moreover that afternoon I cycled to work for the first time in ages since getting ill. The committee meeting went well and marked a major step in my recovery.

By **Lewis Wolpert**, Professor of Biology as Applied to Medicine
Anatomy dept, University College
Gower Street, London WC1E 6BT



Professor Florian Holsboer

Amino acid sequence of Substance P

Research on depression
at the Max-Planck Institute of Psychiatry in Munich
By **Florian Holsboer**, director

Stress Hormones

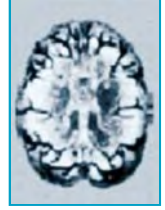
NOVEL TARGETS FOR ANTIDEPRESSANTS

Whenever we experience a situation which puts extraordinary demands on the body, our stress hormone system becomes activated. An early signal of a response to stress is the enhanced release of a peptide called corticotropin-releasing hormone (CRH) from the limbic system, a brain area implicated in the generation of mood and anxiety. CRH in turn stimulates the production of the well-known stress hormone cortisol, which, after entering the blood circulation, prepares the body for coping with the stressful condition. Cortisol release is elevated during an infection, acute psychic trauma or chronic stress. Both hormones, CRH and cortisol, are major players in coordinating the response to stress, and there are many biological checks and balances to keep this control system intact.

Researchers at the Max-Planck Institute of Psychiatry in Munich have found that the stress hormone controlling system is impaired in patients with depression and, to a minor degree, in members of families who have a high genetic susceptibility for developing a depression. Investigators tested whether the brain-derived stress hormone, CRH may also induce behavioural signs and symptoms that are characteristic of depression. Many studies, including studies in humans, rats and mice, indicate that CRH produces behavioural changes that mimic the psychopathology of depression. For example, elevated CRH concentrations in the brain increase anxiety, impair cognition, reduce appetite, sleep and sexual interest, all of which are cardinal symptoms of depression.

The effects of CRH are mediated by a specific receptor (CRH 1 type). Employing

molecular genetic techniques, a mouse mutant was developed that lacks this particular CRH type 1 receptor. In these mice the psychological response to stress is blunted, i.e. they are less anxious and less cognitively impaired when stressed. These experiments suggest that cardinal symptoms of depression can be related to an enhanced function of the CRH system in the brain that results in the symptoms of depression. The depressogenic effect of CRH can be blocked by drugs that prevent its action at the CRH receptor. Such compounds have now been identified, and one of these substances is currently being studied at the Max-Planck Institute of Psychiatry to validate the postulated antidepressant efficacy.



Seasonal Affective Disorder (SAD)

BRIGHT AND CHEERFUL

The Brits, in particular, are always moaning about the weather but for some people grey skies during short winter days really present a major difficulty. Seasonal Affective Disorder (SAD – an appropriate acronym) is a specific sort of depression affecting one in 25 Britons alone and is caused by light deprivation. The cure, logically is sunlight. If, like birds, we could migrate to a warmer climate all would be well.

Apart from the practical problems of leaving the country for six months, for many people, the condition is undiagnosed. Patients, themselves, do not recognise the symptoms and wonder why they want to curl up and forget the world, blaming their woes on their jobs, their partners and the hassle of daily life.

Some research revolves around two hormones in the brain, melatonin and serotonin and how these relate to the body's own biological "clocks" – known as circadian rhythms. The body's rhythm is naturally adjusted by the Earth's patterns of night and day. This rhythm is determined by the activation of two hormones. Melatonin influences a variety of daily cycles, such as sleep, and is derived from serotonin, a hormone that affects our moods.

"Light therapy is the first treatment in psychiatry to evolve directly out of modern neuroscience", says Professor Anna Wirz-Justice from the University of Basel. The treatment is in the form of a device that emits artificial sunlight. In the majority of patients, exposure appears to be beneficial with more than 60 percent in one study recovering from their depression. There is some scepticism with criticism levelled at the possible "placebo" effect of light therapy. However, Professor Wirz-Justice and other experts around the world believe it may prove to have a place in the treatment of a range of related disorders, such as non-seasonal depression, sleep disorders, pre-menstrual tension, and for situations where body cycles are disrupted – jet lag and shift work, for instance.



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