Horizon – The Keys of Paradise, Monday 9.30 BBC2
Mind, Matter and Mechanism, Tuesday 9.30, Wednesday 7.15, Thursday 7.15 Radio 3

A recent discovery which has revolutionised understanding of how the brain works is examined in Monday's *Horizon* and Thursday's programme in Radio 3's series. British scientists found that the brain contains natural opiates; these and related chemicals may ultimately enable us to deal – and tamper – with stress, schizophrenia, pain, sex. **Jo Durden-Smith** looks at the enkephalins and endorphins

Changing our minds

Thou hast the keys of Paradise, O just, subtle and mighty opium!
THOMAS DE QUINCEY

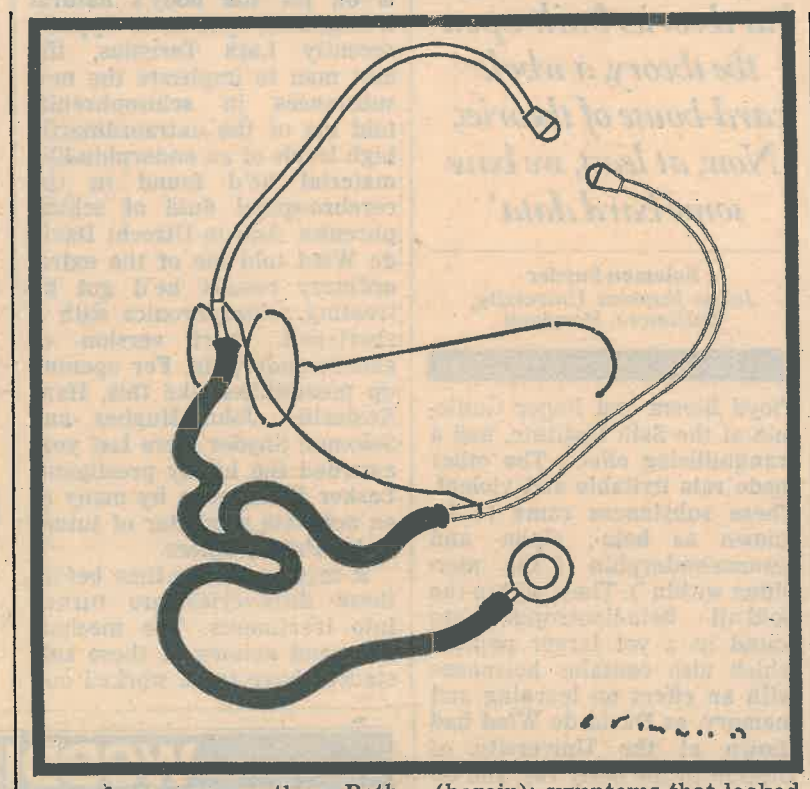
SCIENCE IS the cutting-edge of the future. It gives us possible versions of how we shall live. And if we ignore it, we not only cut ourselves off from an important human aspiration. We give scientists an unaccountable power-in-isolation that they do not want. And we condemn ourselves to a renewed and deepening sense

'In the future we will be allowed to exercise a direct influence by means of particular chemical substances upon the amounts of energy and their distribution in the apparatus of the mind'

Sigmund Freud

of alienation as the scientific future becomes the inevitable technological present.

Nowhere is this clearer than in the story of the enkephalins and the endorphins, tiny chemical drops recently found in the great seas of the brain and the blood. For these drops have brought together the scattered disciplines of hormone and brain science into a broad-front assault on the understanding of madness, pain and addictive behaviour of all kinds. They have given researchers keys that may unlock the doors of perception, personality and psyche. And they promise to deliver up to us new ways to treat the central diseases of our age: schizophrenia, stress, depression and anxiety. Within their gift too, though, they may bring something else: a new power to manipulate at will the affects and abilities, the pleasures and drives at the root of our difference from one another. Both futures are possible, and pure science cannot choose between them. That is up to us.



In *The Odyssey*, Helen gives Telemachus a draught of wine and opium, to relieve him of the pain of his father's loss. And this is where the story begins, with psychotropic, mind-altering drugs, some of which have been known to man for thousands of years. It wasn't until quite recently, though, that we knew what happened when these drugs entered the brain and the nerve pathways to it. Nor did we begin to understand until recently why they produced the effects and side-

'We are bringing back psychiatry to medicine, where it belongs'

Solomon Snyder
Johns Hopkins University, Baltimore, Maryland

effects that they did: euphoria and analgesia, depression of respiration and impotence (heroin); symptoms that looked like acute schizophrenia (amphetamine); relief of schizophrenia (chlorpromazine); symptoms that mimicked psychosis (alcohol and LSD); and, above all, addiction. Scientists, in fact, knew very little about the way the brain worked at all. And these substances, simply because they had such dramatic and precise effects, looked like very useful tools with which to probe its mysteries.

The most useful were the family of chemicals related to opium, the opiates, because the family had so many members, with mixed, opposite or no effects. When they did have effects, they were also among the most *powerful* of chemicals. Etorphine, for example, which is 10,000 times more powerful than morphine, can be given, to effect, in tiny doses. And naloxone, an antagonist, can rescue addicts from seemingly terminal overdoses within seconds. Scientists argued that the two drugs must work at the same, highly-defined sites, the one producing the narcotic symptoms, the other blocking their expression.

In the late 60s and early 70s, new supplies of money came together with new techniques and technologies, some of them drawn from nuclear and radiation physics. And in 1973, in a highly competitive atmosphere, three groups, Candace Pert's and Solomon Snyder's at Johns Hopkins University, Lars Terenius's at the University of Uppsala and Eric Simon's at New York University, established how the opiates achieved their effects. They zeroed in on target cells in the brain and nervous system, and they attached there to what are known as receptor sites. Receptor sites are large protein molecules that float on the surface of the body's cells and lock on to one – and only one – of a number of naturally-occurring substances, like hormones, which cause different chemical instructions to be sent to their various internal machineries. What the opiates were doing, in other words, was breaking into the nerve cells' lines of communications, interrupting and subvert-

'Many people believe that the finding of the enkephalins was the most important discovery ever made in British pharmacology'

Hans Kosterlitz
Unit for Research on Addictive Drugs, University of Aberdeen

ing their normal signalling processes.

How were they able to do this, though? For man was not born with morphine in him. (Nor was the 350,000,000-year-old hagfish, which had much the same system.) Were they displacing a natural messenger chemical, a neurotransmitter which was also a *natural opiate*?

In 1970, at Aberdeen University, Hans Kosterlitz and John Hughes had begun speculating about the existence of ⟶ 10

9 ←⋘ such a natural opiate. In 1971, they developed an elegant system for testing for opiates. In 1973, encouraged by a California experiment in which Huda Akil and David Mayer had taken part, they started fractionating thousands of pig brains to see if they could find the body's own morphine.

They did. And in 1975, again in hot competition with labs across the world, among them those of Snyder, Terenius and Avram Goldstein, they announced what it was. 'It' was two short peptides, strings of amino-acids, which they christened 'enkephalins' (from the Greek for 'in the head'). They added that the sequence of one of them could be found in a longer amino-acid string, a hormone found 11 years before in the pituitary, called beta-lipotropin.

It was a brilliant piece of

'A number of these peptides will be used in the future to improve people's mental performance, primarily in those who have deficiencies in this respect, like the elderly or children with minimal brain damage'

David de Wied
University of Utrecht, The Netherlands

work, and an extraordinarily important discovery. For it opened up the possibility of new non-addictive analgesics. And it opened up to explanation the effects and side-effects of the opiates. Perhaps the enkephalins were involved not only in natural analgesia (like that experienced by a badly wounded soldier), but also in pleasure, breathing, sex and madness.

The observation about beta-lipotropin was equally important. For a subsection of it, also containing the enkephalin, had recently been found in pigs (by Derek Smyth of the Medical Research Council) and in camels, which are notoriously impervious to pain. Was it, too, a natural pain-killer? It was. It also produced what looked like catatonia in rats. And two of *its* subsections had opposite effects. One, in work done by

'For years, since Freud's general theory, we have had nothing but theories built upon the theory, a whole card-house of theories. Now, at least, we have some hard data'

Solomon Snyder
Johns Hopkins University, Baltimore, Maryland

Floyd Bloom and Roger Guillemin at the Salk Institute, had a tranquillising effect. The other made rats irritable and violent. These substances came to be known as beta-, alpha- and gamma-endorphin ('the morphine within'). They, within the hold-all beta-lipotropin, are found in a yet larger peptide which also contains hormones with an effect on learning and memory, as David de Wied had shown at the University of Utrecht in the early 70s, and on the fight-flight response.

Pain, memory, tranquillity, irritability, intensity and madness: hormones and what seemed a neuro-transmitter: behaviour and the brain. Suddenly peptides, which were thought to operate, by and large, outside the brain and nervous system, became all-important. Conventional wisdoms were overthrown. The barriers between the brain sciences began to evaporate.

The **Horizon** film reveals how

'It's been very exciting. It's almost been like science fiction'

Candace Pert
National Institute of Mental Health, Bethesda, Maryland

the endorphins have since been shown to be involved in acupuncture and electrical stimulation and even in the success of placebos: in addiction, chronic pain and even childbirth: how their study has led to new treatments and, perhaps, to the first non-addictive powerful analgesic. It traces the chemical connections between pain, schizophrenia, obesity and sex.

For the rest, it is only possible here to hint at the range of research in the field. Peptides have been experimentally used as attention-concentrators and possible treatments for amnesia and senility. The hunt is on for the body's natural tranquilliser system. In Uppsala recently Lars Terenius, the first man to implicate the new substances in schizophrenia, told me of the extraordinarily high levels of an endorphin-like material he'd found in the cerebro-spinal fluid of schizophrenics. And in Utrecht David de Wied told me of the extraordinary results he'd got by treating schizophrenics with a shortened, inert version of gamma-endorphin. For opening up possibilities like this, Hans Kosterlitz, John Hughes and Solomon Snyder were last year awarded the highly prestigious Lasker Prize, seen by many as an accurate predictor of future Nobel Prize winners.

It may be a long time before these discoveries are turned into treatments. The mechanisms and actions of these substances have to be worked out. Experiments have to be repeated and confirmed. But, once again, science has given us a glimpse of the future: a future in which we may be able to manipulate into relief and cure the delicate chemistry of pain and brain disorders: and one in which, less promisingly, we may have control over mood and pleasure and the differences between us. De

'What we are talking about is personality and disorders of personality being broken down to the interplay of chemical molecules'

Lars Terenius
University of Uppsala, Sweden

Quincey's opium does not have the keys to paradise. But it has given us important keys to the life of the mind and what we may be able to do *with* it and *to* it. ●

WODDIS ON...

A Simple Man

'There is no room for ugly mathematics.'
What matters is the beauty of his mind.
He smoked his pipe, played Mozart, left his socks off,
Went sailing and left Newton far behind.

Why should a dead man so command affection,
Whose thoughts to most are still a foreign tongue?
Perhaps because he looked the stage professor,
Made little jokes and stubbornly stayed young.

$E = mc^2$ – a neat equation.
Energy, mass, velocity of light.
Posterity may think he was mistaken;
The Japanese can prove that he was right.

Are time and distance absolutely constant?
The question nagged him like an aching tooth.
Shifting his vision, ever the observer,
He closed his eyes and tried to see the truth.

Today's beliefs we hold and take for certain
Tomorrow we shall certainly renounce.
He knew the thinking man can only measure;
It's commonplace humanity that counts.

ROGER WODDIS

(Einstein's Universe, Wednesday 7.5 BBC2)

* in documentry U said endorphins where X6 higher ~~the~~ in pregnant women than in non-pregnant.