New substance helps to identify Alzheimer's at an early stage

Visualizing **memory loss**

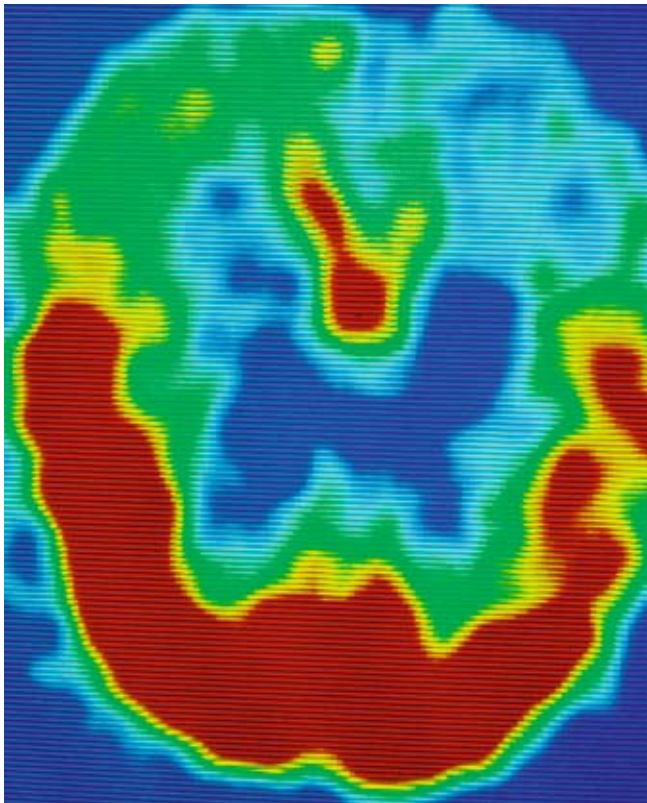
Alzheimer's: a harsh diagnosis, for patients and their families alike. Up to now, however, it has only been possible to definitely confirm the presence of the disease after death. But Bayer HealthCare research scientists want to change that: they are developing novel substances for imaging processes which will make it possible to identify the commonest form of dementia at an early stage.

What day is it? Where are the car keys? What's this thing called again? Almost everyone experiences everyday situations in which they have forgotten something or they can't think of the right word. When difficulty in remembering words, memory loss or behavioral changes become more and more serious over the years, a pathological memory impairment may be the reason: dementia. The most common form of dementia (Lat. demens: to be without mind, confused) is Alzheimer's disease or Alzheimer's type dementia. With this insidiously developing disease of the brain, the nerve cells slowly but inexorably die off. The brain shrinks, with the result that brain functions in affected individuals deteriorate. In the early stages, they suffer from impairment of memory and orientation. Experts refer to these deficits as "mild cognitive impairment" (MCI). Later, sufferers no longer recognize family and friends. This is followed by a complete loss of the powers of judgment and personality. In many patients, the disease can drag on for up to twenty years. Alzheimer's disease is not part of the normal ageing process and it is followed inevitably by death: at present, there is no cure for Alzheimer's and it is impossible to diagnose it with certainty, especially in the early stages.

"The lack of clinical procedures for a reliable early diagnosis often leads to the disease only being recognized at a late stage, placing a burden on relatives. The lack of an early diagnosis is also a considerable barrier, both to the treatment of affected patients and the development of new therapies," explains Dr. Ludger Dinkelborg, Head of Molecular Imaging Research at the Bayer Schering Pharma Division in Berlin.

Almost 18 million Alzheimer's patients worldwide

Over a million people suffer from this typical age-related disease in Germany alone. About four percent of all 60- to 70-year olds are affected and one in four of those over 85 are sufferers. It is estimated that there are over 24 million



Gradually increasing confusion: Alzheimer's patients (left) suffer a deterioration of their mental capacities. Protein deposits in the brain (shown in red, right) which lead to the slow death of nerve cells and the loss of brain mass are believed to be responsible.

dementia patients worldwide, 75 percent of them with Alzheimer's disease.

Experts expect the number to double over the next 20 years, in view of increased life expectancy, rising to around 80 million dementia patients by the year 2040. In view of these figures and estimates, the importance of reliable diagnostic procedures and effective treatments continues to increase.

Protein deposits cause brain mass to shrink

This is precisely the problem, however: although patients currently benefit from drug products which mitigate the symptoms of the disease and slow down its progression, there is no cure for Alzheimer's. In everyday practice, doctors like Erlangen-based Alzheimer's specialist Professor Jens Wiltfang have to rely on a time-consuming exclusion process. The methods used at present allow only a description of the condition and function of the brain: "One-hundred percent reliable diagnosis is only possible after death with an autopsy," explains the deputy director of the Erlangen Psychiatric and Psychotherapy Clinic (see Interview).

One of the causes of Alzheimer's disease is believed to be protein deposits or plaques. "In the brain, these protein deposits overlay each other like layers of leaves," explains Dinkelborg. Because of their chemical structure, these deposits are called beta-amyloid plaques. It is assumed that they are formed when certain elements become detached from the walls of nerve cells and then join together to form protein particles outside the cell. These particles disrupt the function of the nerve cells and trigger inflammation of the affected area of the brain. This leads ultimately to the death of the nerve cell and the disappearance of brain mass.

Although traditional imaging procedures such as computed tomography (CT) and magnetic resonance imaging (MRI) are already used in the diagnosis of dementia, the results they give are still unsatisfactory. Memory problems are not always synonymous with Alzheimer's. The dividing line between normal age-related memory loss and dementia is often fluid, making a clinical diagnosis difficult. In fact, there are several causes of dementia: "Vascular changes in the brain can also be the cause," explains Wiltfang. These vascular causes are particularly common in patients with high blood pressure and diabetes. Since each disease needs its own specific treatment, reliable diagnosis is crucial.

Support could now be available for doctors in their quest to distinguish clinical syndromes more precisely, in the form of a new non-invasive method of examination which is currently in the development phase at Bayer Schering Pharma: molecular imaging. A team led by Bayer research scientist Dinkelborg is testing a substance which will identify

Alzheimer's disease: "We bind a radioactive fluorine-18 atom to a molecule which subsequently accumulates on the protein plaques in the brain. The deposits in the brain can then be visualized by positron emission tomography (PET) and Alzheimer's disease is diagnosed on the basis of objectively measurable data." The imaging radioactive molecules, known technically as tracers, make the early identification of Alzheimer's easy: "They dock directly on to the amyloid plaques and so locate the main culprits, the time bomb which is ticking in the patient's brain," says Professor Wiltfang of the Bayer development, which should allow early and clear diagnosis.

Fluorine-18 compound makes Alzheimer's visible early on

The fact that the "Bayer tracer" is able to bind to these protein deposits in the brain at all is due to the special characteristics of these radioactive substances. The fluorine-18 labeled molecule, known as AV1/ZK (BAY 94-9172), is so tiny that it has no problem crossing the blood-brain barrier. In addition, the radioactive isotope F-18 has a half-life of just under two hours. "After about 20 hours, i.e. after more than 10 half-lives, the radioactive fluorine has almost entirely disappeared from the body," says Dinkelborg. Because of the very high detection sensitivity of this non-invasive imaging technology, only a very tiny dose needs to be injected. "No side effects have been observed in the studies carried out to date," reports Dinkelberg. AV1/ZK was synthesized by Professor Hank Kung, a chemist at the University of Pennsylvania, Philadelphia, USA, and reached Bayer Schering

Signs of dementia

- *Problems of orientation: those affected are often unable to find their car in the car park or they get lost when out walking.*
- *Disappearing short-term memory: forgetting names, appointments or when to take medication.*
- *Behavioral changes: withdrawal from friends and relatives, increased irritability and reduced tolerance, depression, agitation, impatience.*
- *Word-finding difficulties: the names of everyday objects such as vases or brushes are forgotten.*
- *Impaired powers of judgment: inability to distinguish the important from the trivial.*
- *Fear of the new, such as moving to a new home and hence an unfamiliar environment.*

Radiochemistry: using the "hot cell" (left), Marion Zerna and Dr. Matthias Friebe (from left) produce the imaging radioactive molecule known as a tracer. Whether the new substance actually attaches to the protein deposits in the brain is then tested in the laboratory.

Alzheimer's researchers (left) Dr. Matthias Berndt and Dr. Matthias Friebe discuss test results in the Bayer Schering Pharma laboratory with their colleague Jana Hannig (right) to whom they hand over the radioactive substance - packed in a special safety container.

Interview

"Incurable, but its progress can be slowed"

Diagnosis of Alzheimer's: *research* spoke to Professor Jens Wiltfang, Deputy Clinical Director and Head of the Research Laboratory for Molecular Neurobiology and Neurochemical Diagnosis of Dementia at the Psychiatric and Psychotherapy Clinic, Erlangen

Why is an early diagnosis so important?

One in two patients with mild cognitive impairment goes on to develop dementia and one in four to develop Alzheimer's. The earlier a differential diagnosis is made using an uncomplicated but reliable method of testing, the more selectively we can instigate the best treatments and so prevent a rapid progression of the disease before the brain is too badly damaged.

Which procedures currently predominate in the diagnosis of dementia?

The three current clinical methods are firstly the physical neurological examination of the patient, including history-taking. Relatives and the family doctor should be involved in this if possible. Secondly, neuropsychological and psychometric tests are carried out with the patient, for example in the form of questionnaires. Imaging procedures also play their part in diagnosis. Computed tomography (CT) or magnetic resonance imaging (MRI) of the patient's head is often carried out. But these procedures have their shortcomings, as although traditional CT or MRI images show reduced brain volume, this is only in advanced stages of the disease. In addition, other diseases of the brain have similar appearances.

What about the treatment of Alzheimer's patients?

In essence, it is a matter of alleviating the symptoms, i.e. improving attention and concentration and moderating delusions, hallucinations, aggression and depression by medication. The result is that the patient is more active and less of a burden on the family.
Two groups of drug products are authorized for the treatment of Alzheimer's. Firstly, products which increase acetylcholine levels, thereby improving the exchange of information by nerve cells and in the early stages stopping the disease for about a year in one third of patients, virtually freezing it. Later, the disease continues unabated, however. Secondly, there is an active substance which improves short-term memory in patients with moderate to severe Alzheimer's disease, but it does not have any delaying effect.

Many doctors advocate a combination of the two drug products. What is your opinion on this?

There are indications that the two substance classes can be successfully combined and synergistic effects achieved. In the sense of "double the amount helps twice as much". And without additive side effects. However, the combination is not often used in practice - for reasons of cost. Relatives should speak to the treating physician about this.

What are the prospects for Alzheimer's treatment in the future?

Research is currently being carried out on various fronts. Active and passive immunization is looking promising. The target of immunization are the plaques which, like viruses or bacteria, are made up of proteins and can therefore be eliminated by the body's own immune system. Initial practical tests have been successful: some immunized patients had fewer plaques in the brain and there were indications that the mental capacities of immunized patients had stabilized. Research is also being carried out with substances which prevent the development of plaques, interrupt the production chain or break them down.

When will Alzheimer's be curable?

I don't think we'll ever be able to cure this disease. I do believe, however, that following intensive research, in five to eight years we will be able to slow it down considerably.

Pharma via the start-up firm Avid Radiopharmaceuticals which is also located in Philadelphia. Professor Chris Rowe, of the University of Melbourne, Australia, who has been a research partner of the company for many years, was the first to try out the substance in humans.

By the time Alzheimer's disease is normally recognized, a great deal has already happened. "The chronic loss of neurons has already been going on for several years, but only becomes apparent as the brain tries to compensate for all the deficits," explains Alzheimer's specialist Wiltfang. All the more important, then, that the pernicious disease should be diagnosed as early as possible. Pilot studies have already shown that the Bayer tracer is well suited for this. "We were able to classify patients clearly as Alzheimer's patients using AV1/ZK," says the qualified physiologist Dinkelborg. Other studies are already planned. According to Dinkelborg, the reliability of this molecular imaging process is due to the fact that "the fluorine-labeled molecules are distributed quickly to the brain via the bloodstream, bind specifically to the pathological plaques, and the unbound molecules are quickly eliminated from the body. Therefore, despite the low level of exposure to radiation, they are easily and clearly measurable by PET."

Rapid authorization expected for the diagnostic procedure

"If we find that a patient has no amyloid plaques in the brain, he probably does not have Alzheimer's disease either, and so does not need specific treatment. When we do diagnose pathological deposits, however, we can make the correct therapeutic decisions at an early stage," says Dinkelborg, describing the clear-cut nature of the innovative diagnostic process.

The extremely small amount of tracer which is administered to the patient – amounts as tiny as millionths of a gram – means that less preclinical preparation is required before its first use in humans than is usually the case with other pharmaceutical products. This "proof of mechanism" process, during which the clinical departments carry out clinical studies at an early stage of development, makes it possible to identify promising research at an early stage and to develop it quickly. "We hope that it may be possible to obtain marketing authorization for this important diagnostic process more quickly than usual," says Dinkelborg.

As harsh as the early diagnosis of Alzheimer's disease may be, it offers the basis for individually tailored therapy. The earlier treatment is started, the better the results which are achieved, leaving sufferers time to make arrangements for their care or settle matters of inheritance and power of attorney with their families.

www.alz.org

Relatives and sufferers can find information on the website of the U.S. Alzheimer's Association, along with the dates of significant events and advice.

Memory lapses: Alzheimer's sufferers often have to note down their daily routines meticulously so that they can manage their everyday lives despite the progression of the disease.

Diagnostic aid: Dr. Ludger Dinkelborg in front of the camera which visualizes the protein plaques in the brain using the Bayer tracer.