'Microbrains' reveal the tactics of tumour cells

Phyllida Brown

SCIENTISTS in Norway and Scotland have identified an enzyme in rats' brain tumours that rapidly breaks down surrounding tissue. They are now trying to find out whether it is possible to stop the cancer cells from invading by blocking the action of the enzyme.

Rolf Bjerkvig and Morten Lund-Johansen at the Gade Institute in the University of Bergen and Garry Rucklidge at the Rowett Research Institute, Aberdeen, have developed a sophisticated *in-vitro* model to study the interaction between tumour cells and normal tissue in the laboratory. The model, or "microbrain", has given them clues to understanding the way that brain tumours grow.

The researchers stress that their studies are still at an early stage and that they still face important puzzles. But they believe that the discovery may one day help to improve treatment for people. They presented their latest work at a recent conference on cancer in Hamburg and will publish further data shortly in the German journal *Acta Pathologica (Berlin)*.

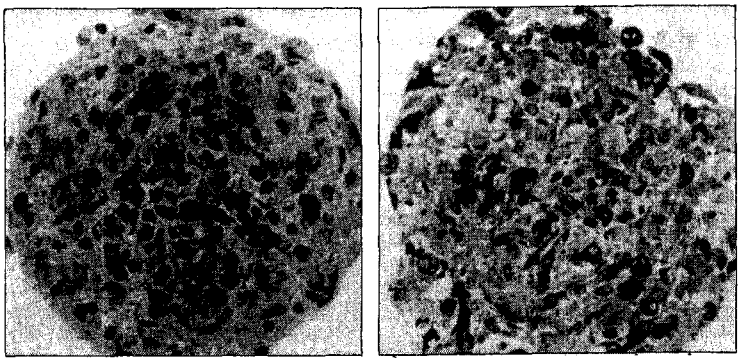
Most brain tumours originate in the glial cells and are known as gliomas. Every year, there are about 2500 new cases, and the outlook for those affected is very poor: few individuals survive longer than a year. Treatment is virtually non-existent, and there have been few advances in research into the disease in a century.

Glioma cells rapidly invade brain tissue, but they almost never spread to the rest of the body. A key element in understanding the disease is to learn how the cells break down healthy tissue and advance into it. But until now this has been difficult to observe in living animals.

Bjerkvig, Lund-Johansen and Rucklidge have found a way round the problem. They have made microbrains—tiny spheres, about 300 micrometres across, that are groups of aggregated single cells from the brains of fetal rats. These microbrains can be developed in culture to produce all the features of a functioning brain, where neurons and glial cells are the key constituents. They also secrete all the "messenger" chemicals, or neurotransmitters, which are responsible for the communication between neurons.

The team has also made model gliomas by creating equally small spheres of cultured glioma cells from rats. When they put a glioma sphere next to a microbrain, the glioma immediately begins to invade the normal tissue. The team has watched the destruction on a time-lapse video. "After four to six days, the brain tissue is completely destroyed," says Lund-Johansen.

The researchers wanted to know what made glioma cells destroy healthy tissue. To find out, they took some of the culture medium that the tumour cells had grown in and added it to the microbrains. It immediately began to destroy them, whereas a control medium that had not contained the cells had no effect. "We came to the conclusion that the tumour cells secreted something into the medium that could cause damage to the microbrain," says Bjerkvig.



The key to destruction: a magnified view (left) of a model brain, made from healthy cells from rats' brains, and (right) the model after it was exposed to an enzyme taken from tumour cells. It is the enzyme that enables malignant cells to destroy healthy tissue

The scientists suspected that the substance that did the damage might be a member of the metalloproteinase family—a large group of enzymes which are important in the remodelling of normal tissue. They have now purified the enzyme and confirmed its identity. Confronted with the pure metalloproteinase, the microbrains "just go to pieces", says Rucklidge.

There are many different types of tumour cell and they do not all behave in an identical fashion. Some are more invasive than other types, for example.

The logical step is to ask whether the breakdown of healthy tissue can be stopped by blocking the action of the enzyme. The team has found that a substance in the body called tissue inhibitor of metalloproteinase (TIMP) blocks the enzyme completely. However, when microbrains were confronted with gliomas in the presence of TIMP, the gliomas still invaded the healthy tissue.

"This suggests that the metalloproteinase cannot be the whole story," says Rucklidge. He speculates that the destruction of tissue and the invasion of tumour cells may be controlled by separate mechanisms. The researchers now want to see what happens when microbrains are exposed to pure metalloproteinase and TIMP.

Now Bjerkvig and his colleague Olav Engebraaten have also analysed biopsies—samples of tissue—from brain tumours in humans. They have found that this tissue invades the microbrains in the laboratory in a fashion similar to the way tumour cells invade the living human brain. The team has also confirmed that the biopsies from humans secrete the metalloproteinase in culture. This model enables doctors to observe the development of a patient's tumour in the laboratory, while the patient is still in hospital. Although hopes of treatment are still distant, this is the first step. □

The physics of a dowsing pendulum

DOWSING, the art of searching for water or minerals using a hand-held pendulum, may really work, according to an Australian engineer. Frank Irons of the University of New South Wales has analysed the chaotic swings of dowsing pendulums. His analysis shows that diviners might be able to detect ore deposits by the variations in the force of gravity they produce (*European Journal of Physics*, vol 11, p 107).

Dowsers rely on changes in the swings of their pendulum to tell them when they are standing above minerals or water. When the pendulum merely swings back and forth, this indicates nothing special. A circular motion, on the other hand, signals success.

According to Irons, dowsers report a characteristic sequence of changes in the behaviour of pendulums when they are held above ore deposits. First the direction of the swings starts to rotate, then the swings turn into an elliptical motion. Finally, the pendulum traces out a circle.

Irons explains this sequence by looking at the forces which drive pendulums. For instance, the steady swinging of a pendulum needs a rhythmic push from the dowser's fingertips to keep it going. Irons says this push can be so small as to be imperceptible even to the dowser.

When it is swinging steadily, the combination of the force of gravity and the drive from the dowser's fingers makes the pendulum sensitive to small changes in the forces acting on it. He believes that the transition from plain swings to the significant circular motion could then be caused either by a slight increase in the tempo of the dowser's rhythmic push or, more importantly, a small fall in the force of gravity. "An increasingly positive dowsing reaction . . . might occur either from an increase in the rate of oscillation of the fingertips . . . or conceivably (and this may be relevant in some instances) from a decrease in the acceleration due to gravity as might occur when traversing an ore body," says Irons.

According to Irons, it would be easy for charlatans to fractionally increase the tempo of their pushes to give the same effect as a change in the force of gravity. He suggests that further studies could identify whether dowsers use finger muscles to alter the pendulum's swing.

Irons' work follows a surge of interest in dowsing-type pendulums because of their chaotic behaviour. In some cases, the motion of a pendulum can become truly unpredictable, and the swinging has become a metaphor for chaos.

William Bown