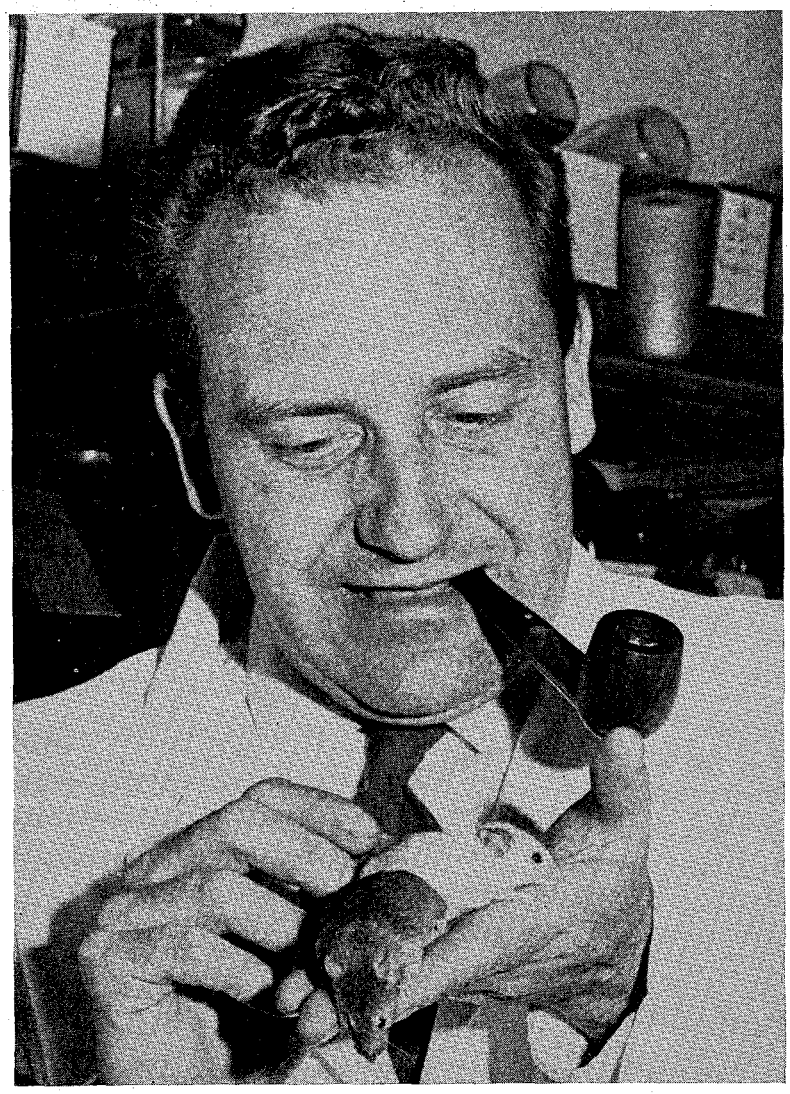


Ray D. Owen, professor of biology, and two of the mice used in his experiments. The darker mouse is an untreated control; the other is lighter because a heavy dose of x-rays has killed the pigment-producing cells in its hair. This mouse survived the lethal dose of radiation because normal blood-forming cells were transplanted into it.

by Ray D. Owen

Facts for a Friendly Frankenstein

When a car or bicycle or washing machine needs repairing you take it to a mechanic with the idea that if he finds a part that is worn out or broken, he will almost always be able to replace that part.

Imagine how important it would be if it were also possible to replace parts of human beings that had worn out, or that had been destroyed by disease, or gone "wild" as in particular kinds of cancer. Within the next hundred years – perhaps rather early in that interval – it is very possible that a lively market will develop for good used parts for the human body.

Of course, the kinds of substitutions of parts now possible are very limited. If a person needs a blood transfusion, it is a simple matter to transfuse the right kind of compatible blood into his veins. But unless his body is able to make the blood he needs, he will require another transfusion soon, and then another. The transfused blood doesn't settle down and make more blood like itself. It is a "dead-end" tissue; it is used up and disappears.

Somewhat similarly, if a person needs to grow bone in a particular place, it is possible to take part of another person's bone and put it in that area, and new bone will often grow there. But this can be done with bone that has been boiled, frozen, or dried. Dead bone works because it provides only the inert scaffolding onto which the host's cells grow, producing more bone of their own.

In fact, there are very few kinds of tissues that can be transplanted successfully from one individual to another, to grow and function in their new home. The reason for this is that the animal body has a kind of machinery to recognize things that are foreign to it, and it responds by destroying these foreign things. This machinery protects us from disease; it aids our recovery from disease; it prevents, generally,

Research in tissue transplantation points the way to a used-parts market for the human body. A transcript of a talk given on Caltech's TV Series, "The Next Hundred Years."

our being reinfected by the same kind of disease-producing organism once we have recovered from a particular disease. This is the machinery of immunity. It recognizes the foreign, invading germ and responds by destroying that germ. When we have a foreign tissue transplant from another individual, the body isn't capable of making a moral judgment as to whether the foreign material is going to be good or bad for it; it recognizes simply that the material is foreign, and responds by destroying it.

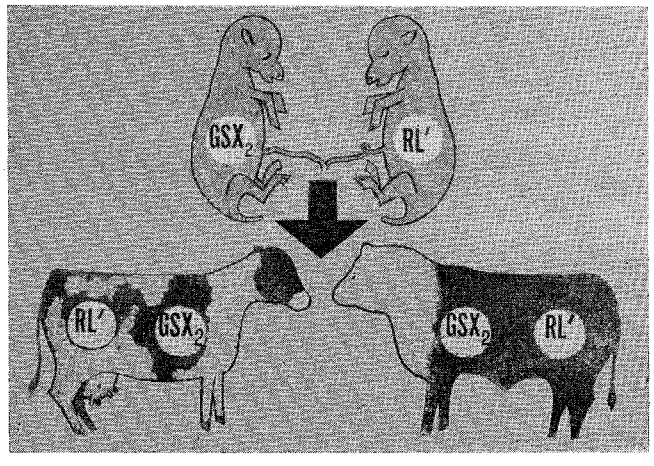
It *is* possible to transplant living, growing, surviving tissue from one person to another – if they are identical twins. Identical twins are so much alike, having the same heredity, that their bodies do not recognize each other's tissues as foreign. But in the ordinary case, if a person has a burn and needs a skin transplant to cover it, the surgeon will take skin from somewhere on that person's own body, because only that skin will be accepted.

So the problem in developing a market for good used parts for the human body is: How can we evade or control the immunological reaction – the recognition and response to foreign material – when there is need for a tissue or organ transplant? We don't have the answer now. But we have some rather promising leads.

One of the leads is, in part, derived from some observations made with my colleagues at the University of Wisconsin about 15 years ago. We were working on blood groups of dairy cattle and a very interesting and unusual case came to our attention. It happened that, on a farm in Maryland, a breeder of purebred Guernseys bred a Guernsey cow one morning to the Guernsey bull on the farm. By accident, that same day the cow was bred again to the beef bull – a white-faced Hereford – on the same farm. At the end of the proper period, the cow gave birth to twin calves. They were a remarkable pair of twins because, while one was a female and looked as a Guernsey should, the other was a bull and had the dominant white-faced marking of the Hereford.

It seemed evident, just from looking at this pair, that they were twins with different fathers. But when we tested their bloods, we found that their blood types were identical. This was hard to believe because they could not have been identical twins; they were of opposite sex, and they apparently had different fathers.

Studying them a little further, we found out why their bloods gave the same reactions. There were two different kinds of blood cells there, just as there should have been for two different individuals. One kind of blood cells was marked with the characteristics we call R and L′, inherited from the Hereford bull. The other kind was marked with the characteristics S and X_2 which came from the Guernsey. This second kind of red cells had G, inherited from the cow, while the first kind did not have G. The cow had therefore evidently produced two eggs, one with G and the other without G, and one of the eggs had been fertilized by a Hereford sperm (RL′), the other by a Guernsey sperm (SX_2). Both of the twins had a mixture of both of these kinds of blood cells. Now,



These remarkable twin calves, one marked like a Hereford, one like a Guernsey, have identical blood types—even though they are of opposite sex, and apparently had different fathers. The mixture of blood cells resulted from the reciprocal transfusions of blood which twin cattle give each other continuously during much of their embryonic lives.

that shouldn't have been so surprising either, because it had been known for a long time that twin cattle usually have a common circulation; their blood vessels join, and they give each other reciprocal transfusions of blood continuously during much of their embryonic lives.

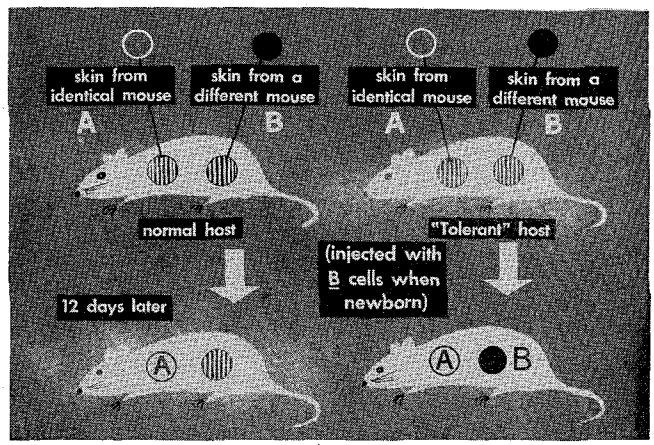
So, we might even expect to find that two calves born as twins have mixed blood. But the surprising thing was that, when we tested these twins again six months later, and again at the end of the year, and again over several years, they stayed the way they had been at birth.

In other words, it wasn't just a matter of blood transfusion, with the transfused blood disappearing. There had been a persistent transplantation of blood-forming tissue between these calves while they were embryos. And this is interesting because it means that when a transplanted tissue is introduced to an individual while he is still very young (in the embryo, in this case) his body is not able to recognize the tissue as foreign, and doesn't respond to it and destroy it. Instead, his body continues to accept this material as his own.

A little while later some people in England showed that it was possible to make skin grafts between non-identical twin cattle. And more recently some Scandinavian workers performed successful kidney transplants. So bovine fraternal twins really lack the ability to recognize what is different in each other.

Not long ago a similar case was found in a human being (below). A "Mrs. McK." came into a British blood bank to give a pint of blood. When the sample was typed, it was found that Mrs. McK. had unusual blood. Her blood behaved mainly as type A, but not all her cells had the A antigen. Quite a large proportion behaved as though they were O. And the O

Mrs. McK, a British blood donor, was found to have an unusual mixture of blood cells. Investigation revealed that she was born a twin, but her brother had died in infancy. Cells from the brother, that had been transplanted into Mrs. McK's body when the twins were embryos, still survived.



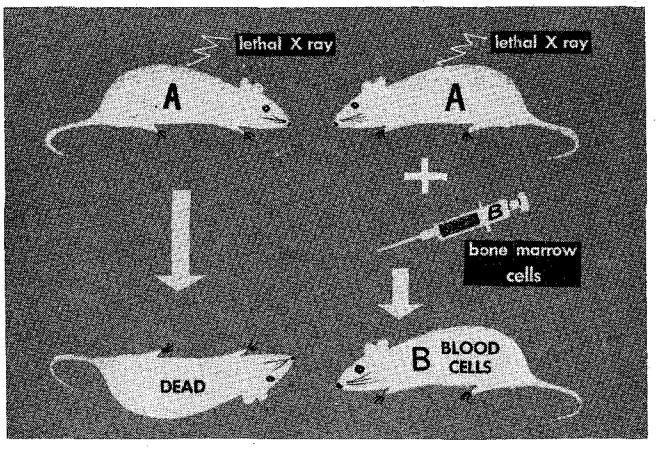
If we put on a mouse of strain A (left) some skin from another member of the same strain, this skin will grow and become accepted, while skin from another line of mice, B, proves incompatible. But if the A mouse had been injected when it was newborn with cells from strain B (right), a transplant of B skin would be completely accepted.

cells lacked another antigen called Kell that was present on the A cells. Her blood was apparently a mixture. Mrs. McK. was asked (with the twin cattle in mind), "Are you by any chance a twin?" "Yes," she replied, "I was a twin, but my twin brother died more than 20 years ago when he was a baby." It was possible to do a complete job of blood typing on the long-dead twin brother because descendants of his cells that had been transplanted into his twin sister still survived in her body, giving rise to blood cells in large numbers. Here again, a successful transplant had occurred because the recipient at the time was an embryo. Of course, Mrs. McK. and her brother were fraternal twins; there is no implication that Mrs. McK. has two fathers.

A few years ago a group of workers in England found a way of putting this kind of situation on a controlled, laboratory basis. These were the same workers that did the skin transplants in twin cattle, mentioned above, but in this work they used mice and chickens. Their procedure is shown above.

If we put on an albino mouse of strain A some skin from another member of the same highly inbred strain, this skin will grow and become fully accepted, just as we would expect when donor and recipient are identical. If we put on skin from another line of mice, B (a colored line this time) then the skin becomes established at first, but within a period of 10 or 12 days the recognition and response machinery has destroyed it and all that is left is a scab where the incompatible skin transplant was put.

Now, suppose the A mouse had been injected when he was newborn with cells from strain B. Cells from a different individual come into the very young animal just as they did in the case of the twin cattle. When an animal that has been treated in this way grows up and is given a B transplant, the skin is com-



If a mouse is given a sufficiently high dose of radiation it will die in a week or ten days. But if, after the x-ray, the mouse is injected with bone marrow cells from another mouse, then it lives.

pletely accepted. The host is "tolerant," so we get a white mouse with a disk of luxuriant, colored hair growing on the tolerated skin transplant.

Does this phenomenon suggest any recipe for *human* practice? Looking ahead in a rather starry-eyed way to the next hundred years, we could say, "Perhaps." It may even happen that when two babies are born, cells will be exchanged between them while they can still accept them, so that each of these babies grows up as a walking "tissue bank" for the other. However, this may well be a situation with dangers in it that we don't recognize, so we would hesitate to attempt such applications to human babies as yet.

There may be special cases where these experiments could be justified. For instance, there are certain kinds of anemia where the person is genetically unable to produce the amount of blood that he needs because of an inherent defect in his blood-forming tissue. If, when this person is a baby, we inject normal blood-forming cells into him from another individual, it might well be that these would be accepted as a transplant to provide a source of normal cells to take the place of his own defective ones.

Actually, the first steps in this research have already been accomplished with mice. Dr. Elizabeth Russell of the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine, by making transplants, has succeeded in saving the lives of mice that are genetically severe anemics.

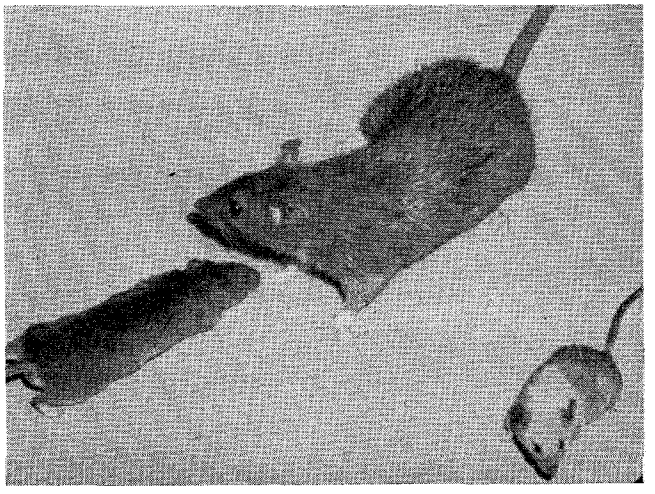
When you look at the broader picture it is obvious that the treating of very young babies in this way is not a general solution to the problem we are discussing. If you need a tissue transplant now because something is badly wrong in you, it doesn't help to say you could have been injected with some kind of cell when you were a baby. What we need to solve this problem is a way of suppressing and controlling the immune response in a normal adult. And it is with that in mind that a great deal of searching is going on now in laboratories all over the world.

Again, we have some leads. One of these is illustrated at the left and deals with very large amounts of x-ray irradiation, or with particular kinds of chemicals which mimic the effects of radiation on animals. If, for example, a mouse is given 900 or 950 roentgens of total body radiation (a very high dose) it will die in a week or 10 days. But if, after the x-ray, this mouse is injected with bone marrow cells from another mouse, then he lives.

This has two points of significance for us. The first is that the life of the mouse has been saved by this kind of treatment. Looking toward a future in which we can expect increased use of high energy irradiation, and possible catastrophes from this, we would be very much interested in saving the lives of individuals who have been exposed by accident to these killing rays.

The second point is that the x-rays have had the effect of permitting the individual to receive a tissue transplant that his body would ordinarily reject. The x-rays, or the chemicals that mimic the effects of x-rays, have inactivated the animal's ability to give an immune response; the recognition and response machinery has been destroyed. So he accepts the tissue transplant that will save his life.

Some examples of animals in this kind of experiment are shown below. First (at the left) there is an ordinary mouse – the well-known mouse-colored mouse. Recently, at Oak Ridge National Laboratory, the second mouse, of this same strain (at the right) was given a lethal dose of x-rays and then injected with bone marrow from a rat (in the center). The second mouse doesn't look really normal because, for one thing, the x-rays have killed the cells in his hair that produce pigment, so the hair is almost white. The x-rays have also had some other effects



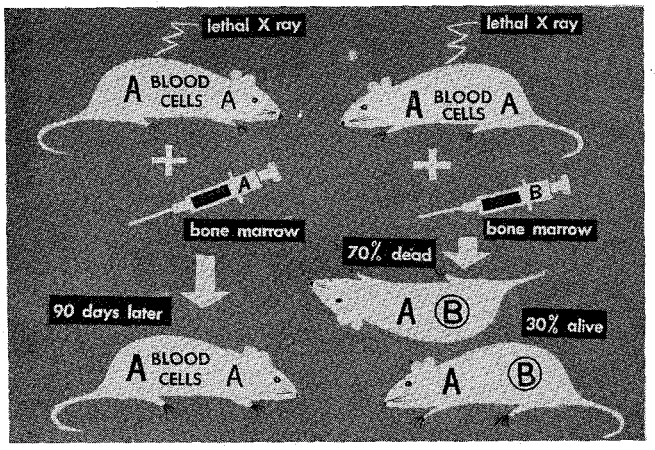
The mouse at the right is of the same strain as the one at the left. Though it looks far from normal, it is remarkable that this mouse is alive at all, for it has been given a lethal dose of x-rays, then an injection of bone marrow from a rat like the one shown in the center.

on the mouse which the injection of bone marrow has not corrected, but the main thing is that this mouse is alive and is reasonably well and happy. And within him are rat blood cells. Now, a rat is a very different kind of animal than a mouse – a different genus and species. It is remarkable that this mouse can live with all of his red blood cells derived from an animal so foreign to him.

This is only one part of the whole story. It is true that the control mouse died from radiation; the bone-marrow-injected one lived. But a lot depends on what has been injected into the irradiated mouse. If a mouse of type A is given a lethal irradiation and then is given A bone marrow (below), he lives almost a normal life for a long period of time. But if he is given a lethal dose of x-ray and then a *foreign* kind of bone marrow (from another kind of mouse or from a rat) then in time he begins to run into trouble. In fact, these mice begin to die off after 30 to 90 days. In 90 days after rat-marrow injection, only 3 out of 10 of these mice are alive. Some may live for a long time, but many of them die. They die from some kind of incompatibility reaction, and we are right back again to the problem of tissue transplantation.

It is believed now by some that the host recovers from the effects of x-ray, becomes able to recognize and destroy foreign matter, and in the process, dies. Others believe that the injected marrow has the ability to recognize that the host is foreign and to react against the host and cause his death. And some people, like myself, believe that there is something of both of these directions of reaction in the delayed death phenomenon.

But the important thing, I think, is that if we are considering extending this kind of treatment to human beings, then we will have to control the delayed death reaction. It may be very useful to save the life of a man by injecting bone marrow from another human being. But we are not doing a very good job if the individual dies from the effects of the treatment after a few months. So, if we are to apply this kind of treatment to human beings, who are very diverse indeed, we have to solve the problem of the delayed incompatibility reaction – and this is a problem for the future.



If a mouse of type A (left) is given a lethal irradiation, and then is given A bone marrow, it lives almost a normal life for a long period of time. But if it is given a lethal dose of x-ray and then (right) is given B bone marrow–from another type of mouse–its chances of survival are reduced.

What are the prospects, then, in this field for the next hundred years? We now have blood banks for blood transfusions. We have some tissue banks for keeping tissues like bone, that don't have to live and grow in a new host. I think we can predict that in the relatively near future we will develop tissue banks for storing the kinds of tissue that need to live and grow in the foreign host. When we do, the vista that opens before us is overwhelming.

Think, for example, of a diabetic – a person who lacks the ability to make insulin in the islet cells in his pancreas. The diabetic goes through his life being injected repeatedly with insulin from animals. How much better it might be if, instead of injecting the insulin, we could provide the diabetic with normal tissue, itself capable of making insulin in the diabetic's body under physiological conditions.

Or take the matter of transplanting healthy blood-forming tissues into the anemic individual. Or suppose we could destroy the diseased cells in leukemia (where a particular kind of cell goes wild) and replace them with normal ones.

Broader horizons

There are many examples that might be cited. But the horizon is even broader than that. If in the course of our search we find ways of controlling the transplantation-immune reaction, the way might open to treatment of many of the more serious aspects of important diseases. Many diseases have bad side effects from the struggle that is going on between the host's immune machinery and the foreign invading germ. In many allergies, as well, the immune machinery goes wrong and causes bad reactions. If we find a way to control this kind of reaction, the diseases of hypersensitivity may come under control, and we can do humanity a great deal of good.

Frankenstein created a monster. Mary Shelley, second wife of the poet Shelley, in the fantasy she published in 1818, had Frankenstein say, "The dissecting room and the slaughter house furnished many of my materials." Our aim, a used-parts market for the human body, is not to create a monster. Instead, we will serve desirable and practical aims – the needs of man. More than that, our effort will be to understand, and in this effort no one can predict what areas of human difficulty will yield to the understanding to be contributed by research in tissue transplantation in the next hundred years, or how far this research will help us to progress to ultimate comprehension of the essential mysteries of life.