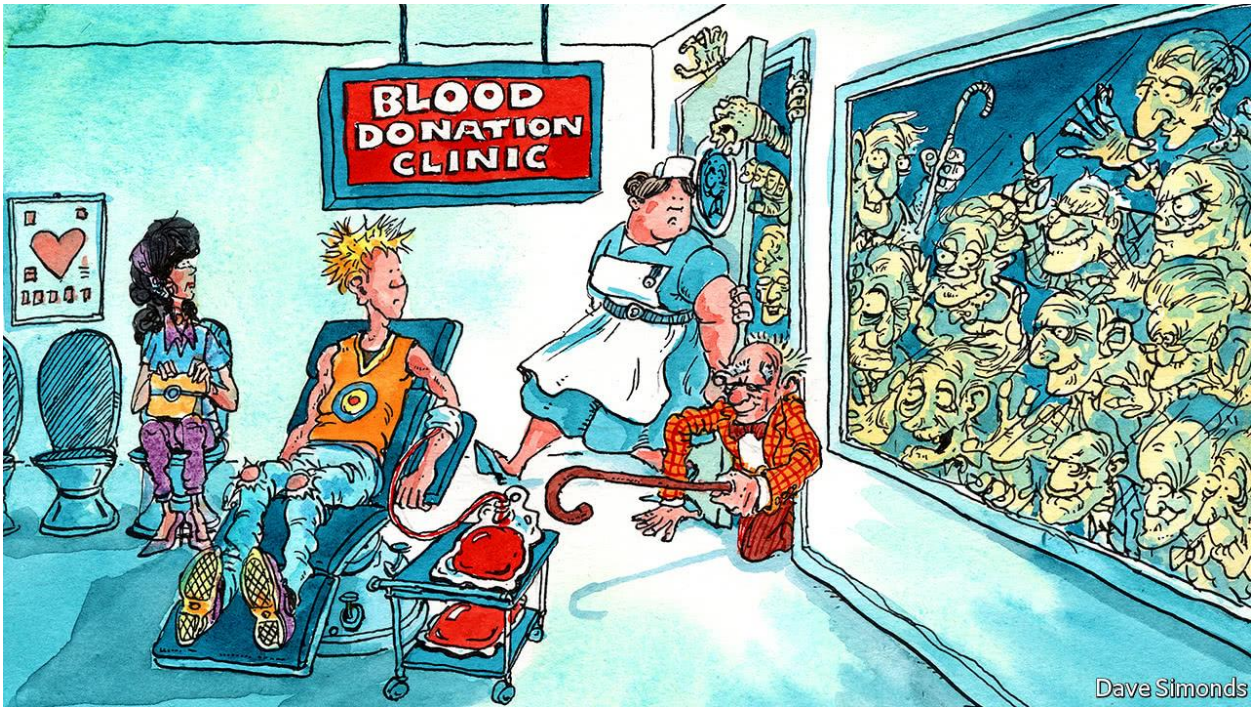
The Economist

Fighting ageing

Blood from young animals can revitalise old ones

Might that be true for people, too?



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Print edition | Science and technology ›

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IT WAS one of the oddest experiments in the history of dentistry. In the early 1950s a researcher called Benjamin Kamrin was looking into the causes of tooth decay. To do so, he turned to that scientific stalwart, the lab rat.

Specifically, he cut small patches of skin from pairs of rats and then sutured the animals together at the site of the wound. After about a week of being joined in this way, the animals' blood vessels began to merge. The result was two rats whose hearts pumped blood around a shared circulatory system. This state of affairs is called parabiosis.

Parabiosis works best on animals that are closely related genetically. By getting his rats to share blood, as well as genes, and then feeding the animals a variety of diets, Kamrin hoped to prove (which he did) that it was sugar in food, and not some inherent deficiency in individuals, that was responsible for rotting their teeth.

Other people, though, have used the technique to find more striking results. For example, mammalian bone density usually drops with age. Three years after Kamrin's work, however, a gerontologist called Clive McCay showed that linking an old rat to a young one boosted the density of the oldster's bones. In 1972 another paper reported, even more spectacularly, that elderly rats which shared blood with young ones lived four to five months longer than similarly old rats which did not.

The rats themselves, unsurprisingly, were not always keen on the procedure. Early papers describe the dangers of "parabiotic disease", in which one animal's immune system rebels against the foreign blood, and also explain how rats must be socialised carefully before being joined, to stop them biting each other to death.

"The technique itself is kind of gross and crude," admits Michael Conboy, a biologist and parabiosis researcher at the University of California, Berkeley. Perhaps for that reason, research had more or less died out by the late 1970s. These days, though, it is back in the news—for a string of recent discoveries have suggested that previous generations of researchers were on to something. The blood of young animals, it seems, may indeed be able to ameliorate at least some of the effects of ageing. And the technique is promising enough to have spawned human clinical trials.

No jokes about vampires, please

This modern interest in parabiosis dates back to 2005, when Dr Conboy (who was then at Stanford University), his wife Irina, and a group of other Stanford researchers published a paper in Nature. In it they described joining mice aged between two and three months with members of the same strain that were 19-26 months old. That is roughly equivalent to hooking a 20-year-old human up to a septuagenarian. After five weeks, the Conboys and their colleagues deliberately injured the older mice's muscles. Usually, old animals heal far less effectively from such injuries than young ones do. But these

mice healed almost as well as a set of young control animals. The young blood had a similar effect on liver cells, too, doubling or tripling their proliferation rate in older animals.

Since then, a torrent of papers have shown matching improvements elsewhere in the body. No one has yet replicated the finding that young blood makes superannuated mice live longer. But it can help repair damaged spinal cords. It can encourage the formation of new neurons in mouse brains. It can help rejuvenate their pancreases. The walls of mouse hearts get thicker as the animals age; young blood can reverse that process as well.

The effects work backwards, too. Old blood can impair neuron growth in young brains and decrepify youthful muscles. Intriguingly, the phenomenon even seems to operate across species. In April Tony Wyss-Coray, also at Stanford, showed that infusing old mice with blood from the umbilical cords of infant humans improved their performance on memory tests.

There have been enough results, says Janet Lord, who runs the Institute of Inflammation and Ageing at Birmingham University, in Britain, to remove any doubt that something impressive is happening. But finding out exactly what is trickier. The working theory is that chemical signals in young blood are doing something to stem cells in older animals.

Stem cells are special cells kept in reserve as means to repair and regrow damaged tissue. Like every other part of the body, they wear out as an animal ages. But something in the youngsters' blood seems to restore their ability to proliferate and encourages them to repair damage with the same vigour as those belonging to a younger animal would.

Nobody yet knows exactly what that something is, but people are looking hard. In all probability, says Dr Lord, it is not one thing at all, but dozens or hundreds of hormones, signaling proteins and the like, working together. Researchers have been comparing the chemical composition of old and young blood, searching for those chemicals that show the biggest changes in level between the two.

These include oxytocin (a hormone better known for its role as a transmitter of signals between neurons); two proteins called GDF-11 and TGF beta-1,

both of which are already known to affect cell behaviour; and B2M, another protein which, among other things, affects the body's ability to absorb iron from food.

Even with a list of targets, working out what is going on is hard, says Richard Lee, a cardiologist at Brigham and Women's Hospital in Boston, Massachusetts. Blood is complicated stuff, and the tools available to analyse it are far from perfect.

Dr Lee's own work is a good example. In 2014 his group suggested GDF-11 as a possible rejuvenating factor. The following year a team at Novartis, a big pharmaceutical company, said that they were unable to replicate those results. The trouble, said the group from Novartis, was that the test used by Dr Lee's team was sensitive to proteins besides GDF-11, messing up the results. Dr Lee's team replied within months that, no, it was in fact the Novartis test that was flawed, because it was itself picking up extra proteins. And there, at the moment, the matter stands.

There are further possible explanations for parabiotic rejuvenation besides blood chemistry. One is that older animals may also benefit from having their blood scrubbed by young kidneys and livers, which mere blood transfusion would not offer. A paper published by the Conboys and their team in 2016, which described blood exchanges that were done in short bursts (thus eliminating the possibility of such scrubbing) reported rejuvenating effects, but ones that were not as widespread as those obtained by full-on parabiosis.

Another idea is that cells from the young animal, rather than chemicals in its blood, could be doing some of the work. By modifying the genes of a mouse so that its cells glow under ultraviolet light, researchers can track where those cells end up when the mouse in question is linked to another. They have found that only a few cells from a younger mouse take root in an older animal it is linked to. This does not quite rule the theory out, says Irina Conboy, for the number of cells may not reflect their importance. Immune-system cells, for instance, multiply rapidly when needed. And they are precisely the sorts of cells that might help an older animal.

The mechanisms by which parabiosis operates, then, are foggy. But that has not dissuaded some companies from setting up trials to see if young blood

can work its magic in people as well as rodents. Persuading patients to have themselves stitched to another person so they can share circulatory systems might be tricky. So instead of full-on parabiosis, these trials are using donated blood plasma.

Blood simples

One such firm, based in California, is called Ambrosia. It has attracted plenty of raised eyebrows for charging its participants, who must be at least 35 years old, $8,000 to join. For that, they get an infusion of blood plasma from a donor under 25.

Most clinical trials work by comparing the treatment under investigation either with another, established treatment, or with a placebo. Ambrosia's trial will not do this. Jesse Karmazin, Ambrosia's founder, says it would be hard to persuade people to pay if there were a chance they might not get the real thing. Instead, he says, patients will serve as their own controls. This will be done by comparing their blood chemistries before and after the treatment.

The unusual trial design, the charge for participation and the sheer amount of hype surrounding anti-ageing research has led some to accuse Dr Karmazin of being more interested in money than science. Not so, he says. Because blood plasma is a natural product, he says, it is not patentable. Without the prospect of a profitable new drug, no drug companies are interested in sponsoring his work.

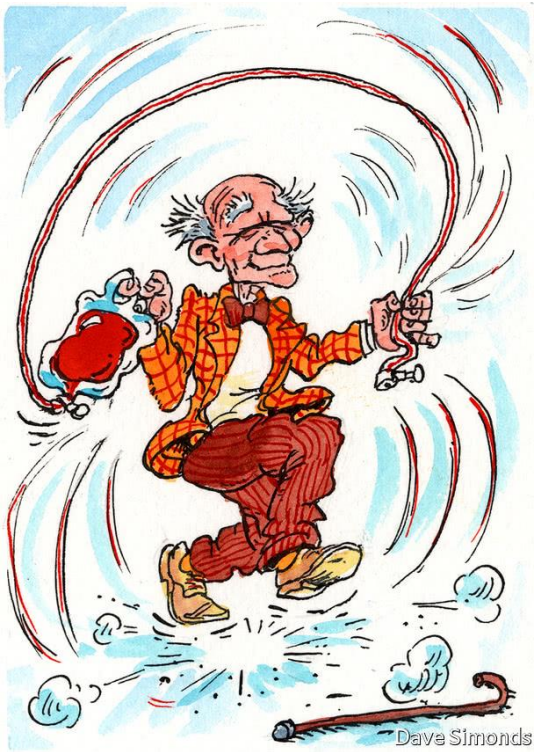
"If I could run this trial for free, I would," he says. "But the reality is I can't." Indeed, Dr Karmazin would not be drawn on how—or if—he plans to turn an eventual profit. But he argues that, with plenty of blood plasma already being collected, both for transfusion and to extract important biochemicals such as clotting factors from it, checking to see if it might have other useful properties is only sensible. Although Ambrosia is not yet ready to publish its results, its initial findings, he says, are encouraging.

Another firm, called Alkahest, which was spun out of work done at Stanford, has had less trouble attracting money. It began its life in JLABS, a biotechnology "incubator" run by Johnson & Johnson, a big drug firm, and has secured $50m from Grifols, a Spanish company that processes blood plasma into various products.

It has commissioned a trial in which 18 people with Alzheimer's disease will be given four infusions of plasma taken from young donors, over four weeks. The main goal, says Karoly Nickolich, Alkahest's boss, is to see if the treatment is safe.

That should, he says, be fairly straightforward. Blood transfusions are, after all, routine procedures. The study will also, though, check whether the blood used can reverse some of the effects of Alzheimer's, as seems to happen in mice in analogous circumstances.

Alkahest plans to present the results of its study at a conference in November. Because the trial is being run by researchers at Stanford, rather than by the firm itself, Mr Nickolich does not yet know what they are likely to show. But if the treatment is safe, he says, and if it proves effective, then the next step will be to identify and isolate the responsible compounds.



Unlike blood plasma, such compounds would be patentable—particularly if they were then made synthetically. And such synthesis would be needed. As Mr Nickolich observes, even if things go well, there is simply not enough donated blood around to treat the world's 44m Alzheimer's patients with plasma extracts.

Some researchers are more wary than Mr Nickolich about the wisdom of such trials. Michael Conboy points out that transfusions are risky. "You can occasionally get immune reactions even with well-matched donors," he says. "In the worst cases you can get full-on anaphylaxis [an extreme allergic reaction that can be fatal]."

For his part, Dr Lee worries about the hype that inevitably attaches itself to "anti-ageing" treatments. "I never use terms like 'anti-ageing' or 'rejuvenation' when I talk about laboratory science," he says. "It conveys a false sense of hope." Dr Lord agrees that talk of reversing ageing is premature. But, she says, there are reasons for cautious optimism. Improving the ability of old muscles to repair themselves, for instance, might not be enough to fend off the Reaper forever. But frailty, and the falls it causes, are a problem for the elderly. Mitigating the damage from Alzheimer's, even if it cannot be cured, would also be a boon.

Rather than lengthening lifespan, says Dr Lord, it is better to think about lengthening "healthspan". That is not immortality. But it would still be quite something.