# Blood Revival: Young Mice Reverse Aging in the Old

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# Blood Revival: Young Mice Reverse Aging in the Old

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**By Alisa G. Woods, PhD**

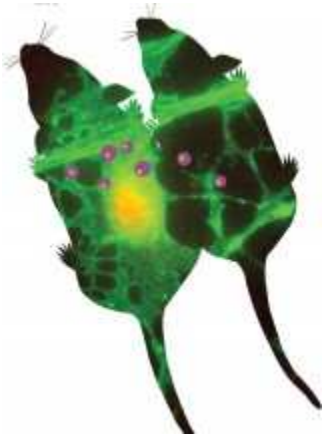
Age may bring wisdom—but it frequently comes with cognitive decline. This can be mild, due to normal aging, or severe, as in Alzheimer disease. Research is increasingly important as life expectancy increases. Aging has numerous brain effects, including decreases in many processes that contribute to plasticity.

**Exchanging blood**

Blood exchange to restore vigor seems like a Victorian medical treatment. The technique, parabiosis, was in fact first tested in the 1860s, according to an article that was published in 1956 by McCay and colleagues[1] of Cornell University. They found that stitching 2 rats together so that their circulatory systems were joined, restored cartilage in the older animal. Recently, there has been renewed interest in parabiosis, along with the goal of determining exactly what in the blood causes youthful resurgence.

Three simultaneously published reports of mouse studies on parabiosis showed that young blood may benefit the old. Researchers observed regeneration of brain and muscle, seemingly via effects on stem cells. The exchange also improved function in the hippocampus: old mice who received young blood became more adept at memory and exercise tasks.

**Improving memory and cognition**



One study appeared in *Nature Medicine*.[2] Aged animals were connected to young mice at the abdomen. The connected pairs are called parabionts. The researchers compared parabionts that were both old (for mice that is 18 months) with old mice connected to young mice. The pairs shared their circulatory systems for 5 weeks.

Following this strange conjunction, the researchers used microarray analysis, a method for examining the expression of several genes at the same time. They specifically isolated the hippocampus. What they found was compelling. In old animals exposed to young blood, there was more expression of genes associated with brain plasticity than is normally seen in old animals that have not received transfusions. Specifically, cells expressed “immediate early genes” in the hippocampus. This may indicate more brain activity and improved memory processing. When the scientists measured hippocampal activity using electrodes (long-term potentiation [LTP], an indicator of memory), they also found increases in LTP in the old animals that had received young blood but not in old animals that had not.

The scientists then looked at the anatomy of cells in the hippocampus of old mice that had received young blood. They found that dendrites were more complex, a possible sign of increased learning. They measured aged mice in standard tests of memory, such as fear conditioning and a water maze, and compared a group of old mice that had received injections of blood plasma with a group of old mice that had not. Both fear learning and spatial memory improved in the group that received the plasma injections.

According to lead author and University of San Francisco Professor Saul Villeda, the finding was partially unexpected: “We knew that there were factors in blood that could rejuvenate stem cells . . . the idea of cognition was surprising.”

**One master regulator—or more factors?**

The investigators used viral vectors, which can block specific genes, to eliminate signaling via CREB (cyclic adenosine monophosphate responsive element binding protein)—a factor that can bind DNA and regulate gene expression. CREB is well known to regulate neural plasticity and memory processes in the brain. They found blocking CREB reduced changes in dendritic spines. Memory improvements also diminished in infused old animals when CREB was blocked. CREB seemed to be highly important for the young blood–induced spine increases and for memory improvements. Although CREB is likely a

“master regulator,” for these processes, Villeda noted that other factors could be involved as well, since “when you block CREB activity you still get a benefit, it’s just not as strong.”

Jennifer Bizon, PhD, a Professor of Neuroscience at the University of Florida, was intrigued by the study. She remarked, “This is an exciting finding with potentially important implications for human aging. The challenge moving forward is how to translate this work to humans.” When asked whether the findings could lead to treatments for memory loss, Bizon responded, “As with any research emerging from rodent models, it takes time to appreciate the potential risks and determine efficacy in humans.”

According to Villeda, this study provides a good example of how basic research in animals can possibly benefit humans. He stated, “At the end of the day our goal is to improve health.” He hopes that the general public will be patient with scientists and understand that the process takes time.

- See more at: http://www.psychiatrictimes.com/geriatric-psychiatry/blood-revival-young-mice-reverse-aging-old/page/0/1#sthash.E7yGpRhM.dpufA group at Harvard has also studied the benefits of young blood for the old. They focused on a specific protein, GDF11, present in young animals but reduced with age. The researchers, led by Professor Lee Rubin and Dr Lida Katsimpardi, found that GDF11 changed blood vessels in the brains of older mice and led to the production of new brain cells.[3] According to Katsimpardi, “I expected the young blood to help the old brain because it makes sense. What surprised me extremely were the blood vessels. I didn’t expect that.”
New neurons can generate in several regions in the adult brain, including the hippocampus, subventricular zone, and olfactory bulb. Many factors decrease neurogenesis, including age, stress, and reduced blood flow. The scientists were interested in understanding whether neurogenesis can be reestablished in aged animals, specifically through effects on the circulatory system.

They first used parabiosis, attaching 15-month-old mice to young ones for 5 weeks, which increased blood vessel branching in the old animals. The blood exchange also induced neurogenesis in several brain regions, including the subventricular zone and the olfactory bulb. Parabiosis improved smell in the old animals, which makes sense because the olfactory bulb processes scents. When very old mice (21 months) were attached to 2-month-old mice, there was a decrease in subventricular zone neurogenesis in the young mice. Something in the old blood was having a detrimental effect. Katsimpardi stated, “Some factors increase with aging and they are toxic. So we know it goes both ways.”

The researchers wanted to understand what might be contributing to youthful renewal. In previous studies, they had identified the protein GDF11 in the blood of young animals but not in the blood of old animals. And, GDF11 was seen in old animals that had received blood from young mice. They decided to inject old mice with either GDF11 or a sham treatment.

The GDF11 acted on the capillary endothelial cells that are needed for blood vessel generation, specifically through the SMAP2/3 pathway. GDF11 also increased neurogenesis in the old animals. The effects were not as dramatic as those seen with parabiosis, which could have to do with the dose that was used. According to Katsimpardi, GDF11 is able to induce half the biological effect of parabiosis. Increasing the dosage of GDF11 might increase its effect.

There may also be other factors at work. According to Katsimpardi, “There are some other candidates and there are some molecules that increase with aging.” More experiments are needed to test this.

Dr Nicole Berchtold, of the UC Irvine Institute for Memory Impairment and Neurological Disorders, speculated about the effects of GDF11 in young animals. She said, “It would be interesting to see if GDF11 injections do the same thing to cognitive function, synaptic genes, etc, as parabiosis did in the aged animals.” Katsimpardi has yet to conduct those experiments.

**Bolstering strength**

Another study led by Professor Amy Wagers tested the effects of parabiosis on muscle stem cells. Connecting the circulatory systems from young to old transformed muscle from an aged state to one characteristic of a younger animal.[4] The improved muscle quality increased strength and endurance.
Older mice that were injected with GDF11 were able to run longer on a treadmill than were control mice. However, GDF11 is not a performance-enhancing protein per se, since younger mice did not become super athletes when injected with it—they ran at the same pace as usual.

Last year the same group published a study showing that GDF11 can rejuvenate heart tissue when injected into older animals, so the effects on running ability could also have to do with having a more vigorous heart and circulatory system.[5]

**Are aging treatments on the horizon?**

Now that GDF11 and CREB-mediated processes have been identified, will drugs that act on them become the new fountains of youth? Katsimpardi feels that the real potential lies in the treatment of neurodegenerative diseases. She states, "The idea is to have a drug that could either prevent or slow neurodegenerative diseases. The most interesting thing for us is not to rejuvenate everyone on the planet, it's more to focus on age-related diseases or vascular diseases."

According to Villeda, researchers are "figuring out a way to translate this into humans. There's a lot more to be done." However, these studies bring promise that science has revealed more about aging and age-related disease.

## REFERENCES


**1.** McCay CM, Pope F, Lunsford W. Experimental prolongation of the life span. *Bull N Y Acad Med*. 1956;32:91-101.

**2.** Villeda SA, Plambeck KE, Middeldorp J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. *Nat Med*. 2014 May 4; [Epub ahead of print].

**3.** Katsimpardi L, Litterman NK, Schein PA, et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. *Science*. 2014;344:630-634.

**4.** Sinha M, Jang YC, Oh J, et al. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. *Science*. 2014;344:649-652.

**5.** Loffredo FS, Steinhauser ML, Jay SM, et al. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. *Cell*. 2013;153:828-839.