in human plasma samples was reported for the first time by Mandel and Metais. During the past several decades, the presence of free-circulating nucleic acids in plasma and serum of healthy and diseased human beings has been a well-established phenomenon.[9] Circulating nucleic acids can be actively released from living cells. Their release into the blood is also thought to be related to dying cells (whether necrotic or apoptotic).[10] In plants, cell-to-cell channels, called plasmodesmata, connect each cell to its neighbours, facilitating the exchange of large molecules. It has been well documented that mRNA, small RNAs and large DNA pieces may move between the cells and around the plant. One can gain some insights by comparing Darwin's gemmules with circulating nucleic acids. Now we can affirm that Darwin's idea that gemmules are the molecular carriers of hereditary characters, multiply by self-replication and circulate throughout the organism has been removed from the position of a provisional hypothesis to that of a well-founded theory. In light of the supporting evidence, is it proper to say that Darwin lacked an understanding of the material basis of heredity, and his Pangenesis has fatal flaws?

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Response to Liu and Li: In defence of gemmules: really?

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In my essay reviewing the Bateson and Gluckman book,[1] I noted in passing that Darwin's theory of heredity (pangenesis) had a 'fatal flaw': that it proposed a model of blending inheritance, which left it open to the critique that innovations would simply be washed out with time.[2] In their letter to *IJE*, Liu and Li ignored the specific point that I made in that sentence and instead cited that statement out of context to promote their own defence of Darwin's pangenesis, and in particular his notion of *gemmules* as a basis of inheritance. This has no bearing on the ideas covered in my review. However, because my essay inspired their letter, I will take this opportunity to briefly respond to their puzzling attempt to revitalize the concept of gemmules.

Darwin's model of natural selection proposed that hereditary traits that improve survival or reproduction will become more common across generations. In the absence of a working understanding of the molecular bases of heredity, which would not come for some decades, Darwin needed to explain (i) how new trait variants arose and (ii) how these variants were passed on to offspring. Pangenesis was his 'provisional hypothesis' to address these issues.[3] He proposed that cells gave off minute hereditary particles (gemmules) that congregated in the sperm and ova to be transferred to offspring. There they aggregated to recreate the same structures from which they were derived in the parent. They could lie dormant across the life cycle and across multiple generations, and the quantity and composition of gemmules with specific properties determined the qualities of the trait that they generated. To Darwin, use and disuse of a structure modified gemmules, and when changed use persisted for several generations, the new changed gemmules outnumbered gemmules generated by the older conditions, leading to the transmission of the newly acquired variations to successive generations.

In retrospect, aspects of pangenesis were closer to the mark than Darwin is often given credit for. In particular, there is a growing consensus that changes in behaviour or activity may be the initial catalyst for the development of new phenotypes, and that this plasticity-induced change can precede the more

gradual process of genetic adaptation.[4] I discussed some of these ideas in my essay. But, there is no need to revisit the mechanism of heredity that Darwin proposed. We now know that cells do indeed harbour hereditary material—DNA—which they obtain from the gametes, but rarely do the gametes obtain extra-nuclear DNA. Interacting with the environment can induce phenotypic change in structures, but there is no evidence that this changes the genome in those cells or that somatic mutations are transferred to sperm or egg.

Even if we accept at face value the findings of the experiments alluded to by Liu and Li,[5] they would not solve the problems that Darwin set out to address in proposing pangenesis. For they primarily purport to show that certain superficial traits, such as feather or coat colour, may in some instances be influenced by circulating DNA. This is interesting, but not likely evolutionarily important, given that the development of these particular traits is not likely influenced by changes in functional demand or activity (the 'conditions of life'), as Darwin's model required to establish new and better-adapted variants. And, there is similarly no evidence that the phenotypic modifications induced by the experiments are incorporated into the germ line.

On the other hand, contemporary work in epigenetics is illustrating some of the ways in which experiences can indeed durably modify gene expression and function. These changes can influence some traits, such as receptor expression and hormonal set points, and at times can be transferred across a generation or two of offspring. We might speculate that some of the modified traits discussed by Liu and Li were induced by epigenetic changes resulting from the experiments themselves, which involved the imposition of acute stress on the animal (i.e. surgical procedures and large transfusions of blood from other species). Whatever we make of these observations, they are very far from the mechanism that Darwin proposed for the transmission of acquired variations, which contemporary understandings of genetics, epigenetics and developmental biology have rendered obsolete. If Darwin were alive today, he would find no need to cling to his speculations about gemmules.

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