

Why we get sick

The new Science of Darwinian Medicine

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SEX AND REPRODUCTION

PREGNANCY

Pregnancy would seem to be the ultimate in shared goals – a refuge from conflict, perfect unity of purpose between mother and fetus. And the relationship between mother and fetus is about as intimate and mutual as any relationship can be. Nonetheless, because mother and fetus share only half their genes, there is conflict aplenty. Whatever benefits go to the fetus help all its genes. The fetus maximizes its fitness by appropriating whatever maternal resources it can use short of jeopardizing the mother's ability to care for it in the future and her ability to raise full or half brothers and sisters (all discounted by the one half or three quarters of genes they do not have in common).

From the mother's point of view, benefits given to the fetus help only half of her genes, so that her optimum donation to the fetus is lower than the amount that is optimal for the fetus. She is also vulnerable to injury or death from the birth of too large a baby. The fitness interests of the fetus and the mother are therefore not identical, and we can predict that the fetus will have mechanisms to manipulate the mother to provide more nutrition and that the mother will have mechanisms to resist this manipulation.

People sometimes argue that there could be no net advantage to a gene that benefits an offspring at a cost to its mother, because its early advantage would be exactly reversed by the later cost. This is not the way things work out. Suppose, in a population in which maternal and fetal interests are served equitably, a gene arises that increases fetal nutrition slightly, at a slight cost to the mother. A fetus that enjoys that advantage can avoid the Cost half the time when it grows up, because only half its offspring will carry the gene. Also, even more obviously, it will pay the cost only if it is female. So the cost would be paid in only about 25 percent of the pregnancies of the next generation. There are additional complexities-which we will not go into - but such quantitative considerations led Harvard biologist David Haig to expect conflict between parent and offspring, even though the ideal contribution from the mother's perspective may be only slightly less than the ideal for the fetus.

Unfortunately, these slight differences create major conflicts. The fetus may be striving mightily to glean an extra few percent of nutrient delivery from the mother, while the mother tries just as hard to prevent this. When the balance of power is disrupted because one participant's efforts are seriously impaired, medical problems arise. For example, the fetus secretes a substance, human placental lactogen (hPL), that ties up maternal insulin so that blood glucose levels rise and provide more glucose to the fetus. The mother counters this fetal manipulation by secreting more insulin, and this makes the fetus secrete even more hPL. This hormone is normally present in all human bodies, but in a pregnant woman it can reach a thousand times the normal concentration. As Haig points out, these raised hormone levels, like raised voices, are a sign of conflict.

If the mother happens to be deficient in her production of insulin, this can cause gestational diabetes, possibly fatal to the mother, and therefore to the glucose-greedy fetus itself. The fetus would have been well advised to curtail its secretion of hPL, but all it can do is play the odds. The average mother is thoroughly competent to produce enough insulin to avoid diabetes, even when flooded by fetal hPL. The evolutionary theory of parent-offspring conflict was worked out many years ago by Robert Trivers, but it was only in 1993 that David Haig applied it to the workings of human pregnancy. It is also only recently that an unexpected but highly relevant genetic phenomenon came to light. Experiments, mainly with mice, have shown that the genes need not rely on the lottery of sexual reproduction to avoid the later costs of special benefits in fetal development. They may resort to genetic imprinting, whereby a gene is somehow

conditioned by its parent either to start acting immediately or to avoid acting in the offspring. Genes from a father may be imprinted so they side with a fetus in the conflict with the mother. These same genes, when they come from a mother, may be imprinted so they have no such effect. The relevance of this to human pregnancy remains to be determined, but in mice, genes imprinted by males produce a fetal growth factor and other genes imprinted by females produce a mechanism for destroying that growth factor. Such evidence suggests that it may not be farfetched to view the womb itself as the battleground on which genes play out their interests at the expense of our health.

Aside from diabetes, another scourge of pregnancy is high blood pressure. This is called preeclampsia when it gets severe enough to damage the kidneys so that protein is lost in the urine. Haig has suggested that this too may result from conflict between the fetus and the mother. In the early stages of pregnancy, the placental cells destroy the uterine nerves and arteriolar muscles that adjust blood flow, and this makes the mother unable to reduce the flow of blood to the placenta. If something constricts other arteries in the mother, her blood pressure will go up and more blood will therefore go to the placenta. The placenta makes several substances that can constrict arteries throughout the mother's body. When the fetus perceives that it is receiving inadequate nutrition, the placenta releases these substances into the mother's circulation. They can damage the mother's tissues, but selection may have shaped a fetal mechanism that takes this risk in order to benefit itself even at the expense of the mother's health. Data on thousands of pregnancies show that moderate increases in maternal blood pressure are associated with lower fetal mortality, and that women with preexisting high blood pressure have larger babies. Further support is provided by findings that preeclampsia is especially common when the blood supply to the fetus is restricted, and that the mother's high blood pressure results from increased resistance in the arteries, not from increased pumping by the heart.

We wonder if the same mechanism may explain some adult high blood pressure. Low-birth-weight infants are especially likely to develop this condition as adults. If genes that are expressed in the fetus to make substances that increase the mother's blood pressure continue to be active, this could cause high blood pressure later in life.

From a traditional medical perspective, these explanations for diabetes and high blood pressure in pregnancy are revolutionary, and unproven, but we suspect they may well prove correct. If so, they provide extraordinary evidence for the power of looking at life from the gene's point of view, for the ubiquity of biological conflicts of interest, and for the practical utility of an adaptationist approach to disease.

Human chorionic gonadotropin (hCG) is another hormone made by the fetus and secreted into the mother's bloodstream. It binds to the mother's luteinizing hormone receptors and stimulates the continued release of progesterone from the mother's ovaries. This hormone blocks menstruation and lets the fetus stay implanted. HCG seems to have originated in the contest between the fetus and the mother over whether the pregnancy should continue or not. Up to 78 percent of all fertilized eggs are never implanted or are aborted very early in pregnancy. The majority of these aborted embryos have chromosomal abnormalities. Mothers seem to have a mechanism that detects abnormal embryos and aborts them. This adaptation prevents continued investment in a baby that would die young or be unable to compete successfully in adult life. It is advantageous for the mother to cut her losses as early as possible and start over, even if this means culling a few normal embryos in order to avoid the risk of nurturing an abnormal one. The fetus, by contrast, does everything it can to implant itself and to stay implanted. Producing hCG is an important early strategy for the fetus to further this goal.

It seems likely that high hCG levels are somehow detected and interpreted by mothers' bodies as a sign of a viable fetus—if it can make enough hCG, it is probably normal. So the embryo, to demonstrate its fitness to the mother, must now make greater amounts of hCG, levels that say as loud as they can, "I am the makings of a great baby." It is also conceivable, as Haig points out, that these high levels of hCG are a cause of nausea and vomiting in pregnancy. Do you think this an alternative to Profet's morning-sickness theory, summarized in Chapter 6? Not if you understand the distinction between proximate and ultimate causes (Chapter 2). The hCG effect could be part of the adaptive machinery that deters ingestion of toxins. Conversely, it may just be an incidental consequence of high hCG levels. Only a well-designed investigation can resolve this issue.