genotype. Intra-locus conflict casts doubt on this possibility. Therefore, understanding the incidence and resolution of sexual conflict becomes important for understanding models of sexual selection.

Additionally, sexual dimorphism, although widespread, need not indicate that conflict has been fully resolved, although it may indicate a partial resolution. What are the constraints on conflict resolution and where do we find them? In cases of sexual dimorphism, how much conflict remains unresolved, and why?

Finally, is mate choice generally rational? In other words, do preferred mates enhance fitness? Or are preferred partners those best able to manipulate their mates for selfish benefit? These are just some outstanding but important questions.

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Primer

Cooperation and conflict in human pregnancy

David Haig

For many humans living today, obstetric care begins early in pregnancy, and most babies are born in hospitals. These are precautionary measures. Medical complications during the brief nine months of pregnancy are such a common part of human experience that we rarely ask ourselves why gestation does not always proceed as smoothly and reliably as the lifelong beating of our heart or filtration of blood by our kidneys. The birth of a healthy child is central to reproductive fitness and must have been subject to strong natural selection. Why then should placentas be less reliable organs than hearts or kidneys? Why should maternal hearts and kidneys be more subject to catastrophic failures during pregnancy than at other times? A crucial contrast distinguishes obstetrics from cardiology and nephrology. The coordinated activities of heart and kidneys take place within an individual comprised of genetically largely identical cells, whereas pregnancy involves an interaction between genetically-distinct individuals whose cooperation is obviated by evolutionary conflicts of interest.

Intergenerational conflict between maternal and fetal genes arises from a fundamental trade-off: mothers can invest more in a particular offspring or redirect resources to production of additional offspring. Because of this trade-off, natural selection acting on mothers favors physiological processes, such as investment in bodily maintenance, that increase the overall number of surviving offspring not necessarily the survival of any particular offspring. These conflicts vitiate the reliable exchange of information between generations. Mothers and fetuses are selected to discount each other's signals. For example, human placental lactogen (hPL) is secreted into the maternal circulation at higher levels than any other protein hormone, yet has minor effects in the mother because babies have been born without complications despite deletion of their hPL genes. Seamless coordination of maternal and fetal physiology is thwarted by a deterioration in evolutionary 'trust'. As a consequence, the physiology of pregnancy lacks the intricate homeostatic feedbacks typical of physiological interactions within a genetically uniform body.

Because of the invasive mode of human placentation, maternal and fetal cells become intermingled at the placental interface. The conventional anatomical division into distinct maternal and fetal bodies is further confused by movement of cells across this interface. As a result, maternal bodies are colonized by fetal cells and fetal bodies by maternal cells. These engrafted, microchimeric cell populations are predicted to influence pregnancy in ways that enhance the fitness of the genetic individual from whom they came, not the genetic individual in whose body they now reside. Microchimerism raises the possibility that other genetic individuals may influence the outcome of pregnancy. Could pregnancy be influenced by cells of the mother's mother or of older offspring that we know to be present in the mother's body? Could some of these cells cross the maternal–fetal interface to become secondarily engrafted in the body of their grandchild or younger sibling?

The maternal–fetal unit is triploid

The trade-off between resource allocation to the fetus or to other maternal activities is also a source of conflict within maternal and fetal genomes. Half of a mother's genome is absent in each and every offspring. Consider a heterozygous mother (*Aa*). Half of the mother's embryos receive haplotype *A* and thus do not contribute to the genic fitness of *a*, and half receive haplotype *a* and do not contribute to the genic fitness of *A*. Haplotype *A* would be strongly advantaged if it could cause mothers to increase investment in embryos with *A* and reduce investment in embryos without *A*, and reciprocally for *a*. The benefits would be greatest if *A* caused the early loss of embryos without *A* because these would be quickly replaced by embryos with *A*. How then is pregnancy possible if half the maternal genome conspires against each and every embryo? The probable answer has two parts. First, most maternal genes lack the ability to discriminate between embryos with and without their

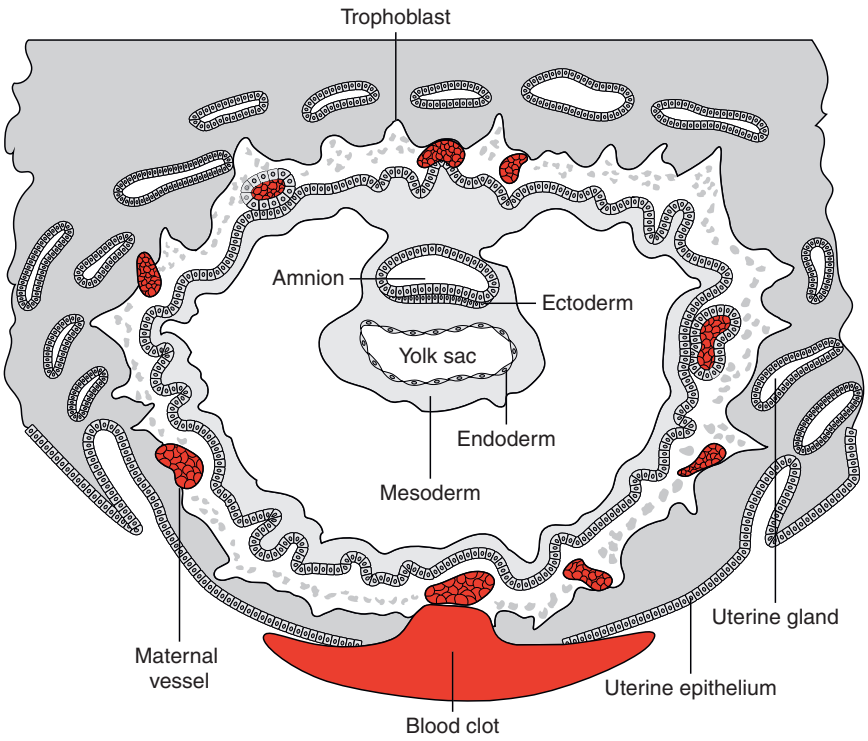

Figure 1. An early human embryo.
At implantation, the human embryo is surrounded by trophoblast that invades maternal tissues including maternal blood vessels. The embryo thus becomes embedded within maternal tissues and can only be eliminated by shedding these tissues. Redrawn after Peters, H. (1899) Ueber die Einbettung des menschlichen Eies und das früheste bisher bekannte menschliche Placentationsstadium. Franz Deutike, Leipzig.

copies. Such genes operate behind a meiotic 'veil of ignorance' that obscures the distribution of their copies among offspring. The best maternal genes could achieve, by actions taken behind the veil, would be to distribute reproductive effort among offspring to maximize the greatest good of the greatest number. Second, nepotistic preferences of alleles that are able to 'peek behind the veil' are opposed by alternative alleles at the same locus and by selection at all unlinked loci.

The meiotic veil of ignorance is partially lifted once genes from mothers are transmitted to offspring because then a gene is definitely present in each offspring in which it is expressed and can direct benefits to this offspring at the expense of its siblings. Behind the meiotic veil, genes expressed in mothers evolve to be impartial among offspring and to allocate resources to maximize the number of surviving offspring, but this impartiality is lost for genes expressed in offspring. A gene of maternal origin expressed in offspring can benefit by reallocating resources from siblings (with an even chance of carrying its copies) to its own offspring (a sure bet).

Suppose that a mother were heterozygous *Bb* and that *B* acting post-zygotically caused fetuses to demand a little more from their mother than did *b*. *B* would thereby receive an 'unfair' share of maternal investment and increase in frequency in the gene pool relative to *b* even though the reallocation of investment reduced the mother's number of surviving offspring. Once *B* was common in the gene pool, most offspring would carry two copies, and the advantages for *B* of increased demand would be absent but the costs for *B* of reduced numbers of surviving offspring would remain.

Adaptations of offspring to increase maternal investment are predicted to decrease the number of surviving offspring.

This 'paradox' is a version of the tragedy of the commons: public goods (in this case maternal care) are over-exploited when multiple agents act independently in their own self-interest. The tragedy is exacerbated for imprinted genes of paternal origin expressed in offspring because mothers sometimes share paternity of their offspring among multiple fathers. A rare paternal gene that acquired a benefit for its own offspring at the expense of a maternal sibling would exchange a sure bet for a less than even chance that its copies would be present in the sibling. Thus, genes that are paternally-expressed and maternally-silent in offspring are predicted to make greater demands on mothers than genes that are maternally-expressed and paternally-silent (with unimprinted genes favoring a compromise).

In summary, the maternal–fetal 'unit' can be conceptualized as having three haploid genomes: a non-inherited maternal genome (absent from the fetus), an inherited maternal genome (shared by mother and fetus), and a paternal genome (absent from the mother). Genes that belong to each genome are subject to distinct selective forces. The conventional genetical division of this triploid entity into diploid maternal and fetal genomes, each of which functions as a coherent whole, involves presuppositions, valid for most but not all loci, that genes expressed in mothers are unable to discriminate among offspring on the basis of offspring genotype and that genes expressed in fetuses have the same effects whether inherited from mothers or fathers.

Embryo selection

The strategic distribution of maternal investment among offspring can be conceptualized as successive decisions whether to invest in an offspring and how much to invest if the first decision is positive. Embryos are cheap. At the time of implantation, mothers are predicted to be 'risk averse' with respect to which embryos are allowed to establish an ongoing pregnancy, because the cost of a delay until the next ovulation is much less than the opportunity cost of raising a child of low fitness. Only slight decrements in the predicted fitness of an embryo, either because external circumstances are not propitious or because of hints of low embryo quality, are sufficient to justify shedding the embryo with the lining of the uterus and starting again with a new embryo. By a fairly conservative estimate, half of all human conceptions never come to term with most losses occurring close to

the time of implantation, before clinical recognition of pregnancy.

The first few weeks after conception are thus the most intense period of mortality in human life history. Embryos will have been subject to strong natural selection to increase their chances of being chosen by whatever tests are set for them by mothers, gradually degrading the quality of information provided by any particular test, and mothers will have been selected to upgrade testing procedures to continue to obtain useful information.

None of our ancestors were sterile. A selective sieve predicts delays in becoming pregnant but not an inability to become pregnant. Therefore, the fact that a substantial fraction of human couples are infertile requires alternative explanations. Some cases of infertility are undoubtedly due to infectious disease and recent deleterious mutations. But interactions among 'nepotistic' alleles that are favored because they cause the loss of embryos without their copies may also contribute to the human burden of infertility. Two regions of the human genome stand out as candidates for nepotistic favoritism at the maternal–fetal interface: the major histocompatibility complex on chromosome 6 and the killer-cell inhibitory receptor complex on chromosome 19. Both complexes are highly polymorphic and have evolved to distinguish 'self' from 'other'. Their primary function is undoubtedly control of pathogens but, from the evolutionary perspective of any extended maternal haplotype, an embryo that lacks its copies is a 'foreign' intruder in the uterus whose elimination would benefit the haplotype.

Once a mother's body commits to provisioning a particular embryo, an evolutionary trade-off arises between investment in the resulting fetus and maintenance of the mother's own body. Maternal maintenance costs have contemporary or delayed benefits for other offspring, in addition to the benefits of a healthy mother for the current fetus. Because most genes expressed in mothers are impartial among offspring but genes expressed in fetuses favor their own offspring over its siblings, fetal genes are predicted to place a thumb on the scale tilting the balance toward greater maternal investment in their own fetus. As a consequence, fetal provisioning is subject to contested control with fetuses attempting to gain more from mothers than mothers have evolved to supply.

Human embryos embed themselves within the uterine wall during the first weeks of pregnancy. From this secure location, their expanding placentas breach maternal arterioles and convert them into large-bore, low-resistance vessels that lack vascular smooth muscle. As the placenta matures, maternal blood is exsanguinated into the intervillous space of the placenta before returning to the maternal circulation via uterine veins that have been similarly breached. This 'hemochorial' arrangement is often assumed to increase the efficiency of nutrient transfer between mother and fetus by reducing barriers between the two circulations, but mothers have not evolved to maximize the efficiency of exchange and the human placenta is not organized as an efficient counter-current exchanger as one finds, for example, in renal nephrons.

The embedding of human embryos within maternal tissues (Figure 1) necessitates the shedding of the uterine lining at menstruation, if unwanted embryos are to be eliminated in the earliest stages of gestation, and also the shedding of maternal tissues with the placenta at parturition. Because the maternal blood vessels supplying the intervillous space are unable to constrict, it is the contraction of myometrial smooth muscle, not the absent arterial smooth muscle, that has the task of staunching hemorrhage after the third stage of labor. This is far from an ideal arrangement. The 'curses' of menstruation and postpartum hemorrhage are collateral damage of the evolutionary struggle for control of maternal physiology during pregnancy. The non-invasive 'epitheliochorial' placentas of dolphins are perfectly adequate for the development of large-brained neonates without the risk of postpartum hemorrhage because the placenta can be shed without a bleeding wound.

Because maternal blood flows through the intervillous space, human fetuses have direct access to the same blood supply as the mother's own tissues and are able to release substances, and cells, into the maternal circulation that can influence maternal physiology at sites remote from the uterus. The loss of vascular smooth muscle from the maternal resistance vessels of the endometrium, and the trophoblast-

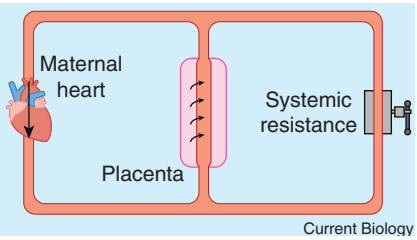

Figure 2. A simplified representation of the maternal systemic circulation.
The placenta releases pressor factors into the maternal blood stream that cause increased resistance in the mother's systemic circulation. Maternal vasoconstriction has the effect of increasing the share of maternal cardiac output that is directed through the intervillous space of the placenta (an arteriovenous shunt) because this sub-circulation is less responsive to the pressor effect.

mediated expansion of these vessels' diameters, limit maternal abilities to control the volume of maternal blood passing through the intervillous space. All these changes are associated with increased fetal influence on maternal physiology and a diminution of the mother's control of her own metabolism. This contest for control creates instabilities in all aspects of the physiology of pregnancy with associated risks of breakdown of homeostasis.

As fetal needs increase toward term, the placenta releases factors into the maternal circulation that increase maternal systemic vascular resistance (Figure 2). This action is predicted to increase blood flow through the intervillous space because the maternal arterioles supplying this space are less responsive to these pressor factors. High doses of one of these factors, soluble FLT1, cause endothelial damage, and associated vasospasm, of the maternal microvasculature. When this process gets out of hand in the serious complication of pregnancy known as preeclampsia, oxygen starvation of maternal tissues due to reduced perfusion can result in failure of multiple maternal organs. For example, placental factors, present at high levels in preeclampsia, may result in hypoxic damage to renal tubules. Excessive maternal blood loss at delivery is another potential cause of reduced perfusion and acute kidney injury.

The risks of pregnancy

Evolutionary anthropologists commonly assume human pregnancy is associated with greater risks for mothers than

occur in other species (although female spotted hyenas might beg to differ because of their high rates of maternal morbidity and infant mortality in first pregnancies). Explanations of human exceptionalism in this regard commonly invoke consequences of bipedalism and large neonatal skulls (we do take inordinate pride in our large brains), but cephalopelvic disproportion is a less important cause of human maternal mortality than postpartum hemorrhage, puerperal sepsis, and preeclampsia.

One unusual feature of human birth was the frequent presence of helpers who assisted mothers and newborns. The survival of most mammalian infants is absolutely dependent upon their mother being able to care for them immediately after birth and this selective premium on maternal health will have acted as a constraint on how much fetuses could demand from their mothers during pregnancy. An evolutionary history of birth attendance may have contributed to the difficulties human mothers now experience during pregnancy because the survival of a baby was no longer tightly dependent on the rapid recovery of its mother after birth. Help was available to support both mother and infant. As a consequence, the indirect costs to babies of increased demands on mothers during pregnancy were relaxed in the human lineage and fetuses responded evolutionarily by increasing their demands.

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Primer

Social immunity in insects

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When animals become sick, infected cells and an armada of activated immune cells attempt to eliminate the pathogen from the body. Once infectious particles have breached the body's physical barriers of the skin or gut lining, an initially local response quickly escalates into a systemic response, attracting mobile immune cells to the site of infection. These cells complement the initial, unspecific defense with a more specialized, targeted response. This can also provide long-term immune memory and protection against future infection. The cell-autonomous defenses of the infected cells are thus aided by the actions of recruited immune cells. These specialized cells are the most mobile cells in the body, constantly patrolling through the otherwise static tissue to detect incoming pathogens. Such constant immune surveillance means infections are noticed immediately and can be rapidly cleared from the body. Some immune cells also remove infected cells that have succumbed to infection. All this prevents pathogen replication and spread to healthy tissues. Although this may involve the sacrifice of some somatic tissue, this is typically replaced quickly. Particular care is, however, given to the reproductive organs, which should always remain disease free (immune privilege).

Similarly, when an ant colony is infected, the contaminated or infected ants, along with their healthy nestmates, fight the infection collectively. A colony of social insects is hence protected by both the individual defenses of its members and a systemic, colony-wide response, providing the colony with a protection known as 'social immunity'. Individual defenses comprise behaviors that prevent pathogen contamination (e.g., pathogen avoidance and self-grooming) and those that fight infections. The latter utilizes the innate immune system, which is capable of raising specific and long-lasting responses, or immune memory ('immune priming'). In addition, entry of pathogens into the colony and infection of individuals is quickly detected by nestmates. These ants will try to remove contaminations from the nest, or from contaminated nestmates, to prevent infection. In cases where infections cannot be prevented, sick individuals may either remove themselves from the colony or are isolated by other ants. Similar to immune cells targeting infected cells, social immunity may also involve the sacrifice of infected colony members. This prevents pathogen replication and spread of pathogens to healthy colony members. Additionally, there is extra protection directed at the queen, the sole reproducing member of the colony.

Metazoan bodies and the colonies of social insects (the social bees and wasps, the ants and termites) are hence protected from disease by strikingly similar principles, despite the fact that they represent very different types of biological organization. A central feature common to both, however, is the presence of a distinct germline and soma. Both are interdependent and require one another for reproduction. In an insect colony, workers are typically sterile themselves, but rear the eggs laid by the queen. Successful colony reproduction relies on both tasks. Even if cells can survive in cell culture when isolated from the body, and individual ants can survive when removed from their colony, reproduction – that is, the formation of new bodies or new colonies – requires cooperation between the subunits of the whole reproductive entity. Due to these organizational similarities, insect colonies are often referred to as 'superorganisms' (Figure 1).

Just like organisms, superorganisms fight disease in a stepwise manner, meaning they employ distinct mechanisms to fight pathogens at the different steps of disease progression. Infectious particles enter the body or colony, establish and begin to spread around the host. This occurs by infecting a cell or colony member, replicating inside them, and then producing transmissible stages that spread to others. Host defenses have evolved to try to break this process at each step. If host defense is successful, the cycle is interrupted and the infection will die out; if not, disease progresses and has to be fought at the next step (Figure 2).

Collective nest hygiene

Even in the absence of pathogens, social insects keep their nests