Genetic Conflict in Human Pregnancy

VOLUME 68, NO. 4 DECEMBER 1993

THE QUARTERLY REVIEW of BIOLOGY

GENETIC CONFLICTS IN HUMAN PREGNANCY

DAVID HAIG

Museum of Comparative Zoology, Harvard University
Cambridge, Massachusetts 02138 USA

ABSTRACT

Pregnancy has commonly been viewed as a cooperative interaction between a mother and her fetus. The effects of natural selection on genes expressed in fetuses, however, may be opposed by the effects of natural selection on genes expressed in mothers. In this sense, a genetic conflict can be said to exist between maternal and fetal genes. Fetal genes will be selected to increase the transfer of nutrients to their fetus, and maternal genes will be selected to limit transfers in excess of some maternal optimum. Thus a process of evolutionary escalation is predicted in which fetal actions are opposed by maternal countermeasures. The phenomenon of genomic imprinting means that a similar conflict exists within fetal cells between genes that are expressed when maternally derived, and genes that are expressed when paternally derived.

During implantation, fetally derived cells (trophoblast) invade the maternal endometrium and remodel the endometrial spiral arteries into low-resistance vessels that are unable to constrict. This invasion has three consequences. First, the fetus gains direct access to its mother's arterial blood. Therefore, a mother cannot reduce the nutrient content of blood reaching the placenta without reducing the nutrient supply to her own tissues. Second, the volume of blood reaching the placenta becomes largely independent of control by the local maternal vasculature. Third, the placenta is able to release hormones and other substances directly into the maternal circulation.

Placental hormones, including human chorionic gonadotropin (hCG) and human placental lactogen (hPL), are predicted to manipulate maternal physiology for fetal benefit. For example, hPL is proposed to act on maternal prolactin receptors to increase maternal resistance to insulin. If unopposed, the effect of hPL would be to maintain higher blood glucose levels for longer periods after meals. This action, however, is countered by increased maternal production of insulin. Gestational diabetes develops if the mother is unable to mount an adequate response to fetal manipulation. Similarly, fetal genes are predicted to enhance the flow of maternal blood through the placenta by increasing maternal blood pressure. Preeclampsia can be interpreted as an attempt by a poorly nourished fetus to increase its supply of nutrients by increasing the resistance of its mother's peripheral circulation.

Unto the woman he said, I will greatly multiply thy sorrow and thy conception; in sorrow thou shalt bring forth children; . . .

Genesis (RSV)

INTRODUCTION

THE MOST INTIMATE human relationship is that between a mother and

The Quarterly Review of Biology, December 1993, Vol. 68, No. 4

0033-5770/93/6804-0001$1.00

her fetus. The fetus obtains all its nutrients and disposes of all its wastes via its mother's blood. It shares every breath that its mother takes and every meal that its mother eats. It draws on the same food reserves when times are hard. During the course of human evolution, different allocations of resources between a mother's needs and those of her fetus will have had profound consequences, particularly when food was limited. The greater the amount taken by the fetus, the greater its birthweight, but the less its mother would have had for other purposes. Lighter babies would have had a reduced probability of survival, but costly pregnancies would have increased the mother's vulnerability to disease, reduced her ability to care for existing children, and decreased her chances of reproducing again. What was best for the fetus would not always have been best for its mother, or so it seems.

Despite this appearance, most biologists have assumed that a mother and her fetus have an underlying harmony of interests because the fetus carries its mother's genes. Put in other words, maternal genes pay the present cost of pregnancy to gain a future benefit, and natural selection acts to increase the benefit per unit cost. In this view, fetal genes could not gain from damage to a mother's health because the child that developed from the fetus would forgo benefits from the continued love and care of a healthy mother.

The argument for harmony is flawed because a mother and fetus do not carry identical sets of genes. As a consequence, genetic actions that enhance the transmission of fetal genes do not always enhance the transmission of maternal genes. An infant's prospects may be bleak if its mother dies, but children have survived without mothers. Thus, if childbirth threatens the lives of a baby and its mother, the baby may struggle for its own survival, even if this increases the risk to its mother. This example is extreme, but conflict may also be expressed in "seemingly felicitous" pregnancies as fetal actions that reduce the probability of miscarriage or that increase the nutrient content of maternal blood.

A potential source of misunderstanding should be addressed immediately. The claim that maternal-fetal relations have been shaped by a history of evolutionary conflict does not imply that either mother or fetus would benefit from a drastic change to the status quo, nor does it imply that the conflict is without benefits. Genetic conflicts have a tendency to escalate, with each move matched by a countermove. Moore and Haig (1991) have likened such situations to a tug-of-war. Two teams attempt to shift a flag a small distance either way, yet there is high tension in the rope and the system would collapse if either side stopped pulling. Similarly, intense conflict can exist between genes in a mother and genes in her fetus even though the difference between their optimal outcomes is small. Moreover, the interplay of opposing forces may be essential for a successful outcome to the pregnancy. Conflict may also become a source of information to both parties. An embryo's ability to overcome maternal resistance gives its mother a measure of the embryo's competence, just as the strength with which a mother resists an embryo's demands may indicate to the embryo how costly these demands are to its mother.

The evolutionary dynamics of move and countermove mean that the details of maternal-fetal relations may diverge rapidly between lineages. Mossman (1937) has remarked that the placenta is probably more variable in structure than any other mammalian organ, and Rothchild (1981) has contrasted the highly variable regulation of the postovulatory follicle (when maternal and fetal genes are vying for control) with the relatively uniform regulation of the preovulatory follicle. The practical consequence of rapid divergence is that information about placentation and maternal responses from one species may be a poor guide for inferences about other species. Further, an adaptive explanation of relations in any particular species is likely to have an idiosyncratic historical component because the order in which rare mutations occur may have been of crucial importance. For this reason, subsequent sections will emphasize evidence from humans. A distinction has traditionally been made between the fetus and its extraembryonic membranes, although both are part of the same genetic organism. Unless otherwise stated, I will use *fetus* and *embryo* to refer to the entire conceptus, including the placenta.

This article has the following plan. In the next section, I present an argument for the existence of *Genetic Conflict* during pregnancy. This is followed by two sections that present background information on *Gestational Anatomy* and *Fetal Growth and Nutrition*. Three ma-

jor sections address the struggle for control of fetal nutrition: AT THE FRONT discusses the placental invasion of the uterine vasculature and maternal countermeasures; BEHIND THE LINES discusses the effects of placental hormones on maternal physiology; PUTTING UP RESISTANCE discusses the hemodynamics of pregnancy. BIRTH AND BEYOND considers the potential for postnatal conflict.

Genetic Conflict

The maternal-fetal relationship has been shaped by natural selection. If one is to understand its evolution, one must consider the fate of genes rather than organisms, because the phenotypic effects of a gene in one organism may affect the fate of the same gene in another organism. For example, whether the genes of a fetus make greater or lesser demands on the fetus's mother may influence the survival of the mother's other offspring.

An economic analogy is helpful. Organisms can be viewed as companies and the genes at a locus as the shareholders of the company. The same gene may have shares in several companies. If they could have their own way, individual investors (genes) would act to maximize their profits from their portfolio of investments, even though these actions need not maximize company profits. In a transaction between companies, there is no conflict if the companies have the same shareholders, but there may be conflict if the shareholders differ. Moreover, conflict can exist among the shareholders of a company if the shareholders have different interests in other companies affected by the transaction.

Suppose that a mother can invest a resource in her current child or retain the resource for a future child. The participants in the transaction are the genes of the mother and of the current child, but the optimal outcome for a gene is determined by whether it is present in the future child. Natural selection acts on the behavior of genes to maximize their expected profits. Three sets of genes have different interests. These are (1) genes in the mother, (2) maternally derived genes in the current child, and (3) paternally derived genes in the current child.

Maternal genes have an equal stake in the current and future child. Therefore, such genes favor transfer of the resource to whichever child will gain the greater benefit. The genes of the current child, however, have a greater stake in the current child than the future child (because they are definitely present in the one, but only possibly present in the other). Therefore, such genes may favor maternal investment in the current child, even if the future child could use the resource more effectively. This idea, that offspring may be selected to take more from a parent than the parent is selected to give, was first clearly expressed by Trivers (1974).

The situation is more complex if mothers sometimes have offspring by more than one father. In this case, paternally derived genes of the current child are less likely to be present in the future child than are maternally derived genes. Therefore, situations can arise where paternally derived genes would maximize their profits if a resource was transferred to the current child, but maternally derived genes would maximize their profits if the resource went to the future child (Haig and Westoby, 1989; Haig, 1992). This complication would be irrelevant if genes retained no information about their parental origin. Genes, however, are known that have different expression depending on whether they are inherited via an egg or sperm (Solter, 1988; Haig and Graham, 1991). Such genes are said to be *imprinted.*

The strict corporate analogy has to be modified to apply to genes because a gene usually has no information about where other copies of itself are distributed, beyond the transmission probabilities defined by relatedness. This has two consequences: (1) A human investor would usually know whether she had shares in the other companies involved in a transaction but, for a genetic investor, complete information is replaced by probabilities. Expected profits can be calculated as if probabilities were fractional shares. (2) At a diploid locus, each organism has two equal shares. The best strategy for a human investor would often be different if she owned both shares in a company rather than one, and she would be expected to adjust her decisions accordingly. A gene, however, is unlikely to change its expression when it is homozygous rather than heterozygous. The initial success or failure of a newly arisen mutation will largely be determined by its effects in heterozygotes. Therefore, successful genes will tend to behave as if the other shareholder were different. Put another way,

genetic strategies only take account of immediate common descent.

Conflicts of interests do not prevent shareholders from cooperating to achieve common goals. For example, in a transfer between companies, it may be in everyone's interest to minimize inefficiency and waste once a price has been determined. Similarly, substantial cooperation can exist between maternal and fetal genes despite conflicts of interest. The implicit metaphor for the genome has often been a machine, of which the genes are components, each with a rigidly specified function. I hope to balance the mechanical model with the metaphor of the genome as a society, of which the genes are the members, sometimes in conflict and sometimes in harmony. The coexistence of cooperation and conflict is a general feature of social organizations, of which the capitalist firm and the human genome are just two examples. I will refer to this social perspective of pregnancy as the *conflict hypothesis* because it is in the recognition of conflict that my views depart most from previous interpretations.

The conceptual distinction between a company and its shareholders means that it is wrong to equate an individual's interests with the (metaphorical) interests of his or her genes. For ease of expression, however, subsequent sections will sometimes be written as if conflict exists between a mother and her fetus, rather than between sets of genes. Such passages should be understood as referring solely to genetic conflicts.

Gestational Anatomy

This section presents background information (and terminology) about the anatomy of the human placenta and uterus. It is based in part on the following works: Noyes et al. (1950) and Ferenczy (1987), who describe the cyclic changes of the nonpregnant endometrium; Farrer-Brown et al. (1970a,b), who describe the blood vessels of the nonpregnant uterus; Harris and Ramsey (1966), Brosens et al. (1967), and Pijnenborg et al. (1980, 1983), who describe changes to the uterine vasculature during pregnancy; Wynn (1967, 1974, 1989) and Ramsey et al. (1976), who describe decidualization and the endometrial response to pregnancy. Accessible accounts of early placentation can be found in Benirschke and Kaufmann (1990), Pijnenborg (1990), and Kurman (1991).

The human embryo implants in the maternal endometrium on about the seventh day after ovulation. A mother often does not know she is pregnant until the failure of menstruation seven days later. In the days following ovulation, the endometrial glands secrete a mixture of carbohydrates and proteins into the uterine lumen. At the same time, the arterioles that supply the endometrium lengthen and become highly coiled. These vessels (which will later bring maternal blood to the placenta) are known as spiral arteries. The maternal tissues that line the pregnant uterus are known as the decidua, because they are shed with the placenta at birth (cf. deciduous). Decidualization is initiated at around the time of implantation. In the decidual reaction, stromal cells enlarge and secrete a tough pericellular capsule. The reaction is at first localized to cells surrounding the spiral arteries, but soon spreads to neighboring cells. If implantation fails to occur, the endometrial glands, spiral arteries, and partially decidualized stroma are sloughed during menstruation, only to be regenerated during the next cycle. The secretory activity of the endometrial glands, the coiling of the spiral arteries, and the initial stages of decidualization will all occur in the absence of fertilization and implantation.

The majority of cells of the first-trimester decidua express leukocyte antigens. The largest single population, outnumbering stromal cells, consists of large granular lymphocytes (LGLs), with smaller populations of macrophages and T cells. The abundance of endometrial LGLs increases dramatically between ovulation and implantation, under hormonal influences. By term, however, LGLs are only a small minority of decidual cells (Starkey et al., 1988; Starkey, 1992).

Before implantation, the human blastocyst differentiates into an outer layer of trophoblast and an inner cell mass. The trophoblast forms those parts of the placenta that make direct contact with maternal tissues, whereas the inner cell mass gives rise to the embryo, the amnion, and the mesenchymal and vascular tissues of the placenta. Two basic types of trophoblast are commonly recognized: mononucleate cytotrophoblast and multinucleate

syncytiotrophoblast. The latter is formed by the fusion of cytotrophoblasts. Syncytiotrophoblast is responsible for the initial invasion of the endometrium, but deeper penetration of maternal tissues is achieved by cytotrophoblasts. These cells sometimes resemble nearby maternal cells (decidua and smooth muscle), but they can be identified histochemically (Angel et al., 1985; Kurman, 1991).

Some cytotrophoblasts invade the endometrium by an interstitial route and aggregate around the maternal spiral arteries. Other cytotrophoblasts invade the endometrium via the lumens of the same arteries. Both interstitial and endovascular cytotrophoblast contribute to the breakdown of the endothelium and smooth muscle of the arterial walls. The walls are replaced by a fibrinoid deposit, without muscular or elastic elements. The arteries are thus converted into distended vessels that are unable to respond to maternal vasoconstrictors. These changes usually extend some distance into the myometrium (Pijnenborg et al. 1980, 1981, 1983; Gerretsen et al., 1983; Yeh and Kurman, 1989; Pijnenborg, 1990). Adrenergic (sympathetic) nerves disappear from the placental site during pregnancy, but cholinergic (parasympathetic) nerves are unaffected (Thorbert et al., 1979; O'Shaughnessy et al., 1992).

As trophoblast breaches the walls of maternal veins and arteries, a system of internal cavities forms within the syncytiotrophoblast. These cavities coalesce and establish continuity with the maternal vessels. After the formation of chorionic villi, this internal cavity of the placenta is known as the intervillous space. The villi are formed when sprouts of syncytiotrophoblast that project into the cavity are invaded by cytotrophoblasts and by cells derived from the inner cell mass. The latter cells give rise to the villous mesenchyme and capillaries. On the maternal side of the intervillous space lies the basal plate of the placenta, in which maternal and fetal cells are intermingled. Brosens and Dixon (1966) have estimated that the basal plate contains the openings of about 120 spiral arteries. On the fetal side of the intervillous space is the chorionic plate of the placenta into which the umbilical cord inserts. An excellent account of placental structure and the organization of the villous trees can be found in Benirschke and Kaufmann (1990).

The intervillous space is the site of exchange between maternal and fetal circulations. Maternal blood enters the space via the modified spiral arteries, is exposed to the villous surface (syncytiotrophoblast), and leaves via uterine veins. Fetal blood reaches the placenta via the umbilical arteries, flows through a capillary net, and returns via the umbilical vein. Fetal and maternal blood are, at all times, separated by a layer of syncytiotrophoblast, a variable thickness of cytotrophoblast and mesenchyme (sometimes absent), and the walls of the fetal capillaries. These cells are all of fetal origin. Therefore, trophoblast can secrete substances directly into maternal blood, but maternal products must cross trophoblast membranes and cytoplasm before they reach fetal blood.

The maternal and paternal genomes of the fetus perform different roles during development. This is most clearly revealed in the aberrant development of human conceptuses with abnormal ratios of maternal to paternal genomes. A *complete hydatidiform mole* is the name given to a conceptus that shows massive proliferation of placental tissues, without an associated fetus. The chorionic villi of a complete mole are usually hydropic (swollen and fluid-filled), without fetal blood vessels (Benirschke and Kaufmann, 1990; Kurman, 1991). Most complete moles are diploid, with both sets of chromosomes paternally derived (Kajii and Ohama, 1977; Wake et al., 1978). Their mitochondrial genome, however, is maternally derived (Azuma et al., 1991). A less extreme phenotype is shown by human triploids. Diandric triploids (*partial hydatidiform moles*) have large cystic placentas. The fetus is well grown with a relatively small head. By contrast, digynic triploids have small noncystic placentas. The fetus is growth-retarded with a relatively large head (McFadden and Kalousek, 1991; Lindor et al., 1992). Thus the paternal genome appears to play a greater role than the maternal genome in placental growth.

Fetal Growth and Nutrition

During early pregnancy, mothers lay down fat to prepare for later pregnancy and lactation. Maternal fat reaches a peak near the end of second trimester, and then declines (Pipe et al., 1979). Thus, well-fed mothers are able

to meet the costs of pregnancy from their daily food intake until the third trimester. A similar conclusion is suggested by birthweights from multiple pregnancies. Quadruplets and singletons have similar weights until 26 weeks gestation; triplets fall behind singletons at 27 weeks; and twins at 30 weeks. Once the growth of individual fetuses falls behind the growth curve for singletons, the weekly increment in "litter" weight is approximately equal for all litter sizes (McKeown and Record, 1953). The mother appears to impose an upper limit on how much she supplies to her offspring.

The nutrient requirements of the embryo are initially small, and are supplied by the secretions of the endometrial glands (a mixture of glycogen, lipids and proteins), probably supplemented by ingestion of the cellular debris that is produced as the trophoblast invades the endometrium (Boyd, 1959). Although the mother is not nutritionally stressed at these early stages, maternal-fetal conflict is predicted, because the number of spiral arteries that are tapped during early pregnancy, before nutrients become limiting, will influence the volume of maternal blood available to the fetus in late pregnancy, when fetal needs are greatest. Circulation of blood through the intervillous space is established by the end of first trimester (Hustin and Schaaps, 1987; Rodesch et al., 1992).

Both the fetus (minus placenta) and the placenta increase in weight throughout pregnancy, but not in constant proportion. A typical fetus has been estimated to weigh 30 g at 12 weeks, 750 g at 24 weeks, and 2750 g at 36 weeks. The corresponding placental weights are 42 g, 210 g, and 425 g. The placenta comprises 85% of combined weight at eight weeks, but only 12% at 38 weeks (Benirschke and Kaufmann, 1990; all dates postconception). Thus, the fetus can be considered to invest most of its income during the first trimester in placental growth, only to recover this investment with interest during second and third trimesters. In general, heavier babies have heavier placentas (Thomson et al., 1969), but the fetus is lighter for a given placental weight if mothers are malnourished (Godfrey et al., 1991). If the onset of growth retardation occurs late in pregnancy, placental growth should be less affected than fetal growth by maternal malnutrition. This would seemingly explain the reduced fetoplacental ratio. Anemic mothers, however, have absolutely heavier placentas than nonanemic mothers despite lower birthweights (Beischer et al., 1970). Perhaps the fetus makes a facultative response to relative starvation by increasing its absolute allocation to placental growth.

Fetal weight curves obscure major changes in body composition (Ziegler et al., 1976; Sparks, 1984). In particular, human fetuses accumulate large amounts of fat during the final weeks of pregnancy. Body composition has been estimated to change from 88.6% water and 0.1% lipid at 24 weeks gestational age to 75.6% water and 9.9% lipid at 38 weeks gestational age (Ziegler et al., 1976). Differences in fat reserves contribute disproportionately to variation in birthweight (Sparks, 1984). For example, fat accounted for 14% of mean birthweight, but 46% of the variance, at an American hospital serving a mostly middle-class population (Catalano et al., 1992). A newborn human may possess 3 to 4 weeks of energy requirements in fat. By contrast, most other mammals are lean at birth (Girard and Ferre, 1982).

AT THE FRONT

"The border zone . . . marks the division between the foetal and maternal tissues. As might be expected it is not a sharp line, for it is in truth the fighting line where the conflict between the maternal cells and the invading trophoderm takes place, and it is strewn with such of the dead on both sides as have not already been carried off the field . . ." (Johnstone, 1914, p. 258). Pathologists of earlier generations often used the imagery of a battlefield to describe the maternal-fetal interface (Fothergill, 1899; Kleine, 1931; Douglas et al., 1959), though none appear to have had theoretical reasons for expecting conflict. Battlefields are often chaotic and confused, with both sides using similar armaments, and with a great deal of seemingly purposeless activity. Interactions at the maternal-fetal interface will probably prove to be similarly complex and difficult to unravel. As an added complexity, the phenomenon of genomic imprinting means that a maternal "fifth column" exists within fetal cells.

Hemochorial Placentation and the Decidual Reaction

Placental morphology is highly variable among eutherian mammals (Mossman, 1937, 1987; Amoroso, 1952; Luckett, 1974). At one extreme, extraembryonic and uterine epithelia are closely apposed, but there is little or no destruction of maternal tissues (epitheliochorial placentas). Examples occur in pigs, horses, whales, and lemurs. At the other extreme, extraembryonic tissues breach the walls of maternal vessels, and the placenta gains direct access to circulating maternal blood (hemochorial placentas). Examples occur in rodents, lagomorphs, insectivores, bats, and, among primates, in tarsiers, monkeys, apes, and humans. Other categories (syndesmochorial, endotheliochorial) have been described, but will not be discussed.

Epitheliochorial placentation is thought to be the ancestral condition of eutherian mammals (Turner, 1876a; Mossman, 1937; Pijnenborg et al., 1985), with secretions of the uterine glands playing an important role in fetal nutrition (Turner, 1876b). Other nutrients are believed to diffuse from the maternal blood stream, across maternal tissue, to the placenta (Amoroso, 1952). Hemochorial placentation appears to have evolved more than

ABBREVIATIONS

AS	Angelman syndrome
BWS	Beckwith-Wiedemann syndrome
CEA	carcinoembryonic antigen
CG	chorionic gonadotropin; hCG (human CG), eCG (equine CG)
DAF	decay-accelerating factor
eCG	equine chorionic gonadotropin
eLH	equine luteinizing hormone
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid, a neurotransmitter
GH	growth hormone
H19	an imprinted gene, closely linked to *IGF2*
hCG	human chorionic gonadotropin; hCGβ (β subunit of hCG)
hGH	human growth hormone (encoded by *hGH-N*)
HLA	principal antigens of the major histocompatibility complex
HLA-G	a trophoblast-specific, nonpolymorphic class I antigen
hLH	human luteinizing hormone; hLHβ (β subunit of hLH)
hPGH	human placental growth hormone (encoded by *hGH-V*)
hPL	human placental lactogen (encoded by *hCS-A* and *hCS-B*)
hTSH	human thyroid-stimulating hormone
IGF-II	insulin-like growth factor-II (peptide); *IGF2* is the human gene, *Igf2* is the mouse gene
IGF2R	human gene for the IGF type-2 receptor; *Igf2* is the mouse gene
IGFBP-1	insulin-like growth factor binding protein-1
LGL	oarge granular lymphocyte
LH	luteinizing hormone; hLH (human LH), eLH (equine LH)
NCA	nonspecific cross-reacting antigen, related to CEA
NK	natural killer; NK cells are a class of lymphocytes
PSβG	pregnancy-specific β_1-glycoprotein, related to CEA
PWS	Prader-Willi syndrome
TGFβ	transforming growth factor-β
TIMP	tissue inhibitor of metalloproteinases
TSH	thyroid-stimulating hormone; hTSH (human hormone)

once as a means by which the fetus gained greater access to maternal nutrients. In the process, uterine secretions have become less important for fetal nutrition, except during the early stages of development.

The genetic-conflict theory predicts that hemochorial placentation has evolved under circumstances where it has been to the marginal advantage of maternal genes to restrict, and of fetal genes to enhance, invasion by trophoblast. If so, one would expect trophoblast to express measures that facilitate the invasion of maternal tissues, and maternal tissues to express defensive countermeasures. This argument does not deny some degree of evolutionary accommodation between maternal and fetal tissues. As trophoblast pushed the front line deeper into maternal tissues, maternal genes would have gained a marginal advantage from mutations that reduced damage to maternal tissues and improved the efficiency of transfer of those resources already lost by the mother. Such changes could occur at the same time as other genes were favored that increased maternal defenses. Thus there is no contradiction in the simultaneous expression of conflict and of coadaptation between maternal and fetal tissues.

Species with hemochorial placentation exhibit strong decidual reactions of the uterine stroma, whereas decidual reactions do not occur in species with epitheliochorial placentation (Mossman, 1937; Amoroso, 1952; Pijnenborg et al., 1985). The conflict hypothesis proposes that the decidual reaction is a maternal adaptation to restrict fetal invasion. This idea is not new. From his studies of "missed abortions," Fothergill (1899) proposed that placenta and decidua were mutually phagocytic, with first the placenta and then the decidua gaining the upper hand. By this means, he conjectured, the invasive potential of the placenta was limited and the mother was protected from excessive damage. Similarly, Frassi (1907, 1908) interpreted maternal leukocytes in the decidua as a means whereby the invasive growth of the parasitic embryo was halted. Gräfenberg (1910) demonstrated the production of proteolytic enzymes by the human embryo, and showed that the decidual transformation of the endometrium was associated with the production of protective "antiferments." Kleine (1931) believed that pregnancy was a biological struggle with a fundamental antagonism between trophoblast and decidua. He cited the association of hemochorial placentation, decidualization, and menstruation as evidence for his view.

A protective role for the decidua has been dismissed *because* decidual reactions are restricted to species with invasive placentas (Robertson and Warner, 1974; Pijnenborg et al., 1985), and *because* decidual reactions are most pronounced in species with highly invasive placentas (Ramsey et al., 1976). Such arguments would be valid if maternal-fetal relations were strictly cooperative. One doesn't argue, however, that antibodies are beneficial to bacteria because they accompany infections. The repeated rejection of a defensive function for the decidua is a good example of how unquestioned assumptions about the absence of conflict have influenced the manner in which "theory-free" data are interpreted.

Decidual tissues, as the name implies, are shed from the maternal body at delivery, at miscarriage, or at menstruation. Although most of the fetal membranes and adjacent decidua are shed at delivery, fetal cells remain at the placental site. The site is undermined by endometrium growing in from the sides, pinched off, and exfoliated into the uterine lumen by the seventh week after delivery (Williams, 1931). The shedding of maternal tissues may have evolved as a means whereby the maternal body rids itself of fetal cells, because, if fetal cells remain, they could continue to manipulate maternal metabolism and behavior. Maternal defenses are initiated before implantation, whether or not pregnancy ultimately ensues. Thus menstruation is possibly another cost that women suffer because of invasive placentation (cf. Kleine, 1931; see Profet, 1993 for a different view of menstruation).

The elimination of fetal cells may not be completely effective. Extravillous trophoblast is found within the myometrium (Pijnenborg et al., 1981), which is not shed, and fragments of trophoblast are regularly deported into the maternal circulation (Douglas et al., 1959; Chua et al., 1991). The fate of deported cells, and their function, if any, is unknown. Women have developed choriocarcinomas,

derived from trophoblast cells, many years after their last pregnancy (Dougherty et al., 1978; Lathrop et al., 1978), but whether such long persistence of fetal cells is common, or a rare aberration, is unknown. Fetal granulocytes and lymphocytelike cells can be isolated from maternal blood from the first trimester until term (Schröder and de la Chapelle, 1974; Wessman et al., 1992), and the lymphocytelike cells may persist in maternal blood for at least a year after delivery (Schröder et al., 1974).

Implantation

Decidual stromal cells secrete a tough pericellular capsule of type IV collagen, laminin, fibronectin, and heparan sulfate proteoglycan (Kisalus et al., 1987; Aplin et al., 1988; Kisalus and Herr, 1988; Zhu et al., 1992). This reaction occurs first around the spiral arteries and then spreads to the rest of the stroma. By this means, decidual fortifications are constructed in the path of the placental invasion. Trophoblasts deploy an arsenal of proteases to breach the decidual barricades (Puistola et al., 1989; U. M. Moll and Lane, 1990; Bischof et al., 1991; Librach et al., 1991; Zini et al., 1992) and decidual cells, in turn, secrete protease inhibitors to impede the advance (Gräfenberg, 1910; Liedholm and Åstedt, 1976; Graham and Lala, 1991).

Cells of the first trimester decidua secrete latent transforming growth factor-β (TGFβ) into the extracellular matrix. TGFβ is activated when placental proteases degrade the matrix. Once activated, TGFβ suppresses placental invasion by promoting the differentiation of cytotrophoblasts into noninvasive syncytia and by upregulating the production of tissue inhibitor of metalloproteinases (TIMP) by trophoblast and decidual cells. TIMP inactivates type IV collagenases and prevents further degradation of the decidual matrix (Graham and Lala, 1991; Graham et al., 1992). Why should fetal genes respond to maternal TGFβ by limiting placental invasion? The conflict hypothesis would be strongly vindicated if the relevant genes are maternally imprinted. The effects of paternally imprinted genes, however, may be opposed by unimprinted genes as well as by maternally imprinted genes (Haig, 1992). Therefore, if paternally imprinted genes contribute to the invasive phenotype of trophoblast, the absence of imprinting at loci that respond to maternal TGFβ would not be a decisive rejection of the conflict hypothesis. TIMP is X-linked and probably behaves as if maternally imprinted, because males have a single (maternal) X chromosome and the paternal X chromosome of females is preferentially inactivated in trophoblast (Harrison, 1989).

The differentiation of cytotrophoblasts into noninvasive cell types is a key event in limiting changes to the maternal spiral arteries. Greater numbers of trophoblastic giant cells are found around intact arteries at the junction of the decidua and myometrium than around arteries that have been highly modified by trophoblast, suggesting that the differentiation of cytotrophoblast into giant cells prevents the transformation of the arterial walls (Gerretsen et al., 1983). The greater the distance that arterial modifications extend into the myometrium, the greater the flow of blood to the placenta. Therefore, the stage at which trophoblasts become noninvasive should be determined by the balance of opposing forces, with maternal and maternally derived genes favoring earlier differentiation and paternally derived genes favoring later differentiation.

Insulin-like growth factor-II (IGF-II) mRNA is present at high levels in invasive cytotrophoblasts, but is absent from syncytiotrophoblast (Ohlsson et al., 1989). Thus, among its other functions, IGF-II may act locally to maintain the invasive phenotype of cytotrophoblasts. The major IGF-binding species of trophoblast membranes is the IGF type-1 receptor, whereas the major binding species of decidual membranes is the 34K insulin-like growth factor binding protein-1 (IGFBP-1) that inhibits the binding of IGF-II to placental receptors (Pekonen et al., 1988). IGFBP-1 is produced by decidualized stromal cells (Giudice et al., 1992), and is first detected in cells surrounding the spiral arteries (Waites et al., 1988). Decidual IGFBP-1 possibly competes for IGF-II with type-1 receptors on trophoblast membranes and thus regulates the invasion of maternal tissues (Bell et al., 1988; Pekonen et al., 1988; Bell, 1989). Birthweights are negatively correlated with the concentration of IGFBP-1 in maternal and fetal serum (Howell et al., 1985; Hall et al., 1986; Wang et al., 1991).

IGF2, the human gene that encodes IGF-II, is expressed solely from the paternal allele in many adult and fetal tissues, including the placenta (Giannoukakis et al., 1993; Ogawa et al., 1993; Ohlsson et al., 1993). *IGF2* is located at 11p15.5 and is closely linked to *H19* (Zemel et al., 1992), a gene of unknown function that is upregulated as human cytotrophoblasts differentiate in vitro (Rachmilewitz, Gileadi, Eldar-Geva, Schneider, de Groot, and Hochberg, 1992). Only one of the two copies of *H19* is significantly expressed in human fetuses (Zhang and Tycko, 1992). Unlike *IGF2*, the maternal allele of *H19* is preferentially expressed (Rachmilewitz, Goshen, Ariel, Schneider, de Groot, and Hochberg, 1992; Rainier et al., 1993). *H19* encodes an abundant transcript that does not appear to be translated into protein (Brannan et al., 1990).

The chromosomal region that includes *H19* and *IGF2* is associated with Beckwith-Wiedemann syndrome (BWS), a fetal overgrowth disorder. Sporadic cases of BWS are sometimes associated with duplications of 11p15, and in all cases the duplicated chromosome is of paternal origin (K. W. Brown et al., 1992; Weksberg et al., 1993). In familial BWS, subjects who inherit the gene from their fathers are less likely to express the condition than subjects who inherit the gene from their mothers (Moutou et al., 1992; Viljoen and Ramesar, 1992). Familial cases could be explained by a mutation that causes inappropriate expression of the maternal copy of *IGF2* (Moore and Haig, 1991).

The homologous loci in mice are also imprinted. *Igf2* (the murine homolog of *IGF2*) is expressed from the paternally derived chromosome in most fetal tissues (DeChiara et al., 1991), whereas *H19* is expressed from the maternally derived chromosome (Bartolomei et al., 1991). Inactivation of the paternal copy of *Igf2* produces neonates that are well proportioned but small (DeChiara et al., 1990). *Igf2r*, the locus that encodes the IGF type-2 receptor, has the opposite imprint to *Igf2*. The paternal copy of *Igf2r* is inactive in mouse embryos (Barlow et al., 1991). A maternal deletion of *Igf2r* is an embryonic lethal in laboratory mice. Embryos with a deleted maternal copy, however, survive and grow to a larger size than their littermates if their father is derived from a wild-caught population (Forejt and Gregorová, 1992). Haig and Graham (1991) have proposed that the IGF type-2 receptor transports IGF-II into lysosomes, where it is degraded. The imprinting status of *IGF2R* in humans is unknown.

Decidual stromal cells produce prolactin, from the late luteal phase onward (Maslar et al., 1979; Kauma and Shapiro, 1986; Ogren and Talamantes, 1988). The function of decidual prolactin is unknown. Josimovich et al. (1977) suggested that prolactin may regulate the volume of amniotic fluid, by analogy to its osmoregulatory effects in fishes and amphibians. Another possibility should be considered. Large granular lymphocytes are the major cell type of the early decidua and proliferate during late luteal phase and early pregnancy (King et al., 1991). Prolactin has recently been shown to act as an autocrine growth factor for lymphocytes (Sabharwal et al., 1992), and the prolactin transcripts of lymphocytes resemble decidual transcripts rather than pituitary transcripts (Pellegrini et al., 1992). Therefore, prolactin may promote the proliferation of decidual lymphocytes. The function of maternal immune cells in the human decidua will be discussed in the next section.

Not all products of the endometrium need be antagonistic to the fetus. The endometrial glands are highly active during early pregnancy, secreting a mixture of proteins, lipids and carbohydrates (Boyd, 1959). These secretions are probably an important source of nutrients for the embryo before circulation of maternal blood is established through the intervillous space. The major peptide product of the glands, pregnancy-associated endometrial α_2-globulin (Waites et al., 1990), is homologous to the β-lactoglobulins secreted by the mammary glands of many mammals (Huhtala et al., 1987). Could this be evidence that uterine and mammary lactation had a common genetic basis in some remote mammalian ancestor?

Fay and Grudzinskas (1991) have reviewed the diverse assemblage of peptides secreted by endometrial cells, only some of which have been considered here.

Immunological Relations

Medawar (1953) formulated the immunological problem of pregnancy as "how does the pregnant mother contrive to nourish within itself, for many weeks or months, a foetus that is an antigenically foreign body?" (p. 324). In this formulation, mother and fetus are implicitly assumed to have a common interest in immune suppression. The theory of maternal-fetal conflict, however, suggests that selective forces are more complex. Complete rejection of the fetus is clearly against maternal interests, except in cases of adaptive miscarriage, but conflict is predicted as maternal tissues attempt to limit invasion by trophoblast. The maternal immune system is faced with the difficult problem of how to distinguish between fetal and maternal cells, when the fetal cells are selected to avoid detection, and of how to modulate responses to allow sufficient but not excessive invasion by trophoblast. ("Sufficient" and "excessive" refer, of course, to maternal interests.) Fetal cells are faced with the equally difficult problem of how to inactivate or avoid immune responses directed against themselves, without compromising maternal defenses against pathogens.

Most cells of the early human decidua are components of the immune system. The largest single population consists of large granular lymphocytes (45% of early decidual cells), with lesser populations of macrophages (19%) and T cells (9%) (Starkey et al., 1988). Endometrial populations of T cells and macrophages remain relatively constant throughout the menstrual cycle, but large granular lymphocytes (LGLs) increase sharply in numbers during late luteal phase (Starkey et al., 1991). Endometrial LGLs possess the antigenic phenotype of highly activated natural killer (NK) cells (Dietl et al., 1992) and are able to destroy trophoblast and choriocarcinoma cells in vitro (King and Loke, 1990; Ferry, Sargent, Starkey, and Redman, 1991; Ferry, Starkey, Sargent, Watt, Jackson, and Redman, 1991). Macrophages are the dominant cell type amidst the fibrinoid debris of the basal plate of third-trimester placentas (Bulmer et al., 1988; Labarrere and Faulk, 1991).

Trophoblast does not express polymorphic class I or class II HLA antigens (Loke et al., 1990; Hunt and Orr, 1992) and is probably invisible to classical HLA-restricted immune responses. The fetal cells that invade the endometrium (extravillous trophoblast) face a different threat because they encounter endometrial LGLs that express an NK phenotype (see above). NK cells are believed to preferentially attack targets that do not express class I antigens (Ljunggren and Kärre, 1990). If so, the complete absence of class I antigens would leave extravillous trophoblast vulnerable to endometrial LGLs. Extravillous trophoblast does, however, express HLA-G, a trophoblast-specific nonpolymorphic class I antigen (Ellis et al., 1990; Loke et al., 1990). King and Loke (1991) have proposed that the function of LGLs is to protect the mother from excessive invasion, and that HLA-G assists trophoblasts to evade these defenses. Extravillous cytotrophoblasts also express decay-accelerating factor (DAF) at their cell surface (Holmes et al., 1990; Hsi et al., 1991). DAF inhibits cytolysis by human NK cells (Finberg et al., 1992), possibly by inhibiting complement activation (Holers et al., 1992; Moran et al., 1992).

Natural killer cell activity of maternal blood is depressed during pregnancy (Russel and Miller, 1986; Lee et al., 1987; Vaquer et al., 1987), and pregnancy sera inhibit T-cell proliferation (Arkwright et al., 1992). The responsible factors are presently unknown, but the pregnancy-specific β_1-glycoproteins (PSβGs) may contribute to the inhibition of maternal immune responses. These placental glycoproteins are released in increasing quantities by the placenta as pregnancy progresses (Klopper, 1980). PSβGs are a group of closely related proteins encoded by a cluster of at least eleven genes at 19q13. The cluster also contains genes for the PSβG-related carcinoembryonic antigen (CEA) and nonspecific cross-reacting antigens (NCAs) (Khan et al., 1992; Thompson et al., 1992). CEA and NCAs function as membrane-bound cell adhesion molecules (Benchimol et al., 1989; Oikawa et al., 1991). The PSβGs are serum proteins but possess the arginine-glycine-aspartate tripeptide that is found on many adhesion molecules (Streydio et al., 1987). An attractive hypothesis is that the soluble PSβGs inhibit immune responses by blocking adhesion receptors on maternal lymphocytes (cf. Zarcone

et al., 1992). NCAs are present on a variety of lymphocyte types (Burtin et al., 1975; Kuroki et al., 1991; Kuijpers et al., 1992) and may be targets of the PSβGs. In support of this hypothesis, CEA-related antigens bind to NCAs and block adhesion of neutrophils to endothelial cells (Kuijpers et al., 1992), and antibodies against NCAs inhibit the lysis of carcinoma cells by activated lymphocytes (Rivoltini et al., 1991).

If a gene expressed in the mother (such as an NCA) interacts with a closely linked gene expressed in the fetus (such as a PSβG), the maternal gene could infer the presence of copies of itself in offspring and preferentially direct resources to these offspring (e.g., by suppressing cytotoxic responses to trophoblast). Such favoritism would be against the interests of other maternal genes that segregate independently of the linked pair. In a formal genetic model, the nepotistic haplotype would have many of the features of an agent of meiotic drive (Haig and Grafen, 1991). Systems of *gestational drive* may play an important role in the evolution of maternal-fetal relations but they will not be considered in this paper, beyond this brief mention.

BEHIND THE LINES

Fetal cells gain direct access to the maternal circulation by their invasion of the uterine vasculature and are thus able to release substances into a mother's blood that have distant effects on her physiology. An important class of substances are placental hormones that act on maternal receptors. I will call such molecules *allocrine hormones* to emphasize that they are produced by one organism to act on the receptors of another.

Allocrine hormones provide a test of the genetic conflict hypothesis. If hormonal communications between a fetus and its mother were strictly cooperative, one would expect natural selection to have increased efficiency and minimized costs. On the other hand, if placental hormones subvert maternal lines of communication, one would expect evidence of an evolutionary escalation. That is, mothers would have been selected to become less responsive to placental hormones and, as a result, fetuses would have been selected to release ever greater amounts. Each escalation would have given a marginal advantage to the relevant gene, and caused it to eliminate less-profligate alleles. If a message can be conveyed in a whisper, why shout? Raised voices are frequently a sign of conflict.

Both hypotheses predict the existence of placental receptors that face maternal blood. From the conflict perspective, these receptors would allow the fetus to gain information about its mother by eavesdropping on maternal endocrine signals. Unlike maternal receptors that can be manipulated by fetal hormones, placental receptors should be relatively immune to manipulation by maternal hormones. The asymmetry exists because the maternal circulation is not a major channel for endocrine communication between *fetal* cells. If a maternal receptor is required for essential endocrine communication between *maternal* cells, maternal signals will be vulnerable to allocrine subversion because the receptor will usually be unable to tell whether a ligand is of maternal or fetal origin. By contrast, placental receptors are not uncertain about a ligand's origin so their responses will be in fetal rather than maternal interests when these interests conflict. More generally, placental physiology is not expected to be directly regulated by maternal signals.

hCG and the Maintenance of Pregnancy

The first physiological decision that faces a newly pregnant mother is whether to carry the child. If the embryo is of low quality, or if the mother is nutritionally (or otherwise) stressed, maternal interests may be served by miscarrying the embryo before substantial resources have been committed. A miscarriage frees, for other uses, resources that would otherwise be expended on the embryo during the remainder of pregnancy and the period of infant dependency. Miscarriage will be adaptive for maternal genes if such genes would gain a greater return by investing the resources in existing or future offspring, of higher quality or produced when conditions are more favorable. For every miscarriage, there will be some investment in time and resources that cannot be recovered. Therefore, adaptive miscarriages are predicted to occur as early as possible during pregnancy to minimize costs.

C. J. Roberts and Lowe (1975) have estimated that 78 percent of human conceptions never come to term. Most conceptions miscarry before the 12th week of pregnancy, many before the first missed menstruation (Edmonds et al., 1982). The majority of spontaneous abortions that can be karyotyped have recognizable chromosomal abnormalities (Boué et al., 1975; Eiben et al., 1987; Plachot, 1989). Such data are consistent with the hypothesis that many miscarriages are the result of an evolved mechanism of quality control (C. J. Roberts and Lowe, 1975).

In a simple model of maternal investment, the optimal strategy for maternal genes is to abort all offspring whose perceived quality falls below some threshold and provision the rest (Haig, 1990). There will be a similar, but lower, threshold below which fetal genes will benefit from the mother investing in siblings rather than the current fetus. Thus, if an offspring's quality falls just below the maternal threshold, the offspring's genes would benefit from the pregnancy continuing whereas maternal genes would benefit from a termination (Haig, 1992). Therefore, genes expressed in fetuses will be selected to take active steps to maintain their pregnancy, and genes expressed in mothers will be selected to avoid manipulation. A theoretical issue that has not been adequately addressed is whether the mother can gain accurate information about fetal quality given that fetal genes may gain an advantage by providing inaccurate information.

Many eutherian mammals maintain their pregnancies by the secretion of progesterone from the corpus luteum in response to luteinizing hormone (LH) released by the anterior pituitary (Hogden and Itskovitz, 1988). A similar system probably operated at some time in our distant ancestry. If so, the fetus has subsequently gained partial control of its fate by becoming the major source of progesterone and "luteinizing hormone" in maternal blood. During the early weeks of gestation, human pregnancy is dependent on maternal progesterone. The placenta, however, has usurped the role of the maternal pituitary by releasing large quantities of human chorionic gonadotropin (hCG) into maternal blood. This hormone binds to the LH receptors of the corpus luteum, prevents regression of the corpus luteum, and stimulates the release of progesterone (W. E. Brown and Bradbury, 1947; Hanson et al., 1971; Dennefors et al., 1982; Hahlin et al., 1989; Jia et al., 1991). hCG also enhances the release of progesterone from syncytiotrophoblast (Bhattacharyya et al., 1992).

Human pregnancies will miscarry if the corpus luteum is removed before the eighth week of gestation, unless the mother is supplied with exogenous progesterone. After this stage, the placenta produces sufficient progesterone to maintain pregnancy despite removal of the corpus luteum (Csapo et al., 1972, 1973). By contrast, removal of corpora lutea at any time during pregnancy causes reproductive failure in hamsters, goats, pigs, and rabbits (Deanesly, 1966).

The concentrations of hCG and placental progesterone in maternal serum during pregnancy can be compared to levels of their endocrine counterparts in the nonpregnant state. Human embryos begin to secrete hCG before implantation (Dokras et al., 1991). The concentration in maternal serum rises rapidly, reaches a peak in excess of 50 IU/ml between weeks 8 and 12, then falls to about 12 IU/ml by week 18, and remains roughly constant until term (Kletzky et al., 1985). Concentrations in fetal serum are less than 5% of maternal levels (Reyes et al., 1974). The high levels of hCG are remarkable when compared to much lower levels of hLH in nonpregnant women. In the "LH spike" that accompanies ovulation, hLH reaches 100 mIU/ml (Hoff et al., 1983). IUs of hCG and hLH are not directly comparable. However, 3.0 IU hCG has the activity of 1.0 IU hLH in a standard rat bioassay (Carayon et al., 1980). Thus concentrations of allocrine hCG reach much higher levels than concentrations of endocrine hLH. Similarly, the corpus luteum secretes 40 to 50 mg/day of progesterone in the midluteal phase, whereas the placenta secretes 250 mg/day at term (MacDonald et al., 1991).

hLH and hCG are dimeric glycoproteins that share a common α subunit but different β subunits. The α subunit is encoded by a single gene on chromosome 6. The β subunits are encoded by closely linked genes at 19q13.3. There is one copy of hLHβ and six copies of

hCGβ (Policastro et al., 1986). At least five of the six hCGβ genes are expressed in the placenta (Bo and Boime, 1992). The ancestral hCGβ appears to have been derived from hLHβ by two frame-shift mutations that have added a 24 amino acid tail to the carboxy-terminus. hCGβ and hLHβ share about 80 percent amino acid identity, and their nucleotide sequences show a high proportion of replacement changes relative to silent and intron changes (Talmadge et al., 1984).

LH is biochemically related to thyroid-stimulating hormone (TSH) and follicle-stimulating hormone (Pierce and Parsons, 1981) and has weak affinity for their receptors (Siris et al., 1978; Carayon et al., 1980). One IU of hLH has the thyrotropic activity of 44 μIU hTSH. hCG has even weaker affinity for the TSH receptor. One IU of hCG is equivalent to 0.25 μIU hTSH (Carayon et al., 1980). Removal of the final four amino acid residues from the carboxyl-terminus of hCGβ increases the thyroid-stimulating activity of hCG threefold (Carayon et al., 1981). These amino acids were added by the second frame-shift mutation in the 3′-tail of the hCGβ gene (Talmadge et al., 1984). LH probably does not have significant thyrotropic activity in vivo, but the high levels of hCG experienced by pregnant women would be extremely thyrotoxic if hCG retained the thyrotropic activity of hLH. Put in other words, hCG production could never have escalated to its current level if there had not been a prior reduction in the hormone's affinity for the TSH receptor. Despite this reduction, hCG may still have significant thyrotropic effects in some pregnancies (Goodwin, Montoro, and Mestman, 1992; Goodwin, Montoro, Mestman, Pekary, and Hershman, 1992; Hershman, 1992). A question that remains unresolved is whether the residual thyrotropic effects of hCG are adaptive for fetal genes or are an unwanted side effect of benefits obtained through the LH receptor.

The hCG that circulates in maternal serum is chemically heterogenous because of various posttranslational modifications (Nwokoro et al., 1981; Kardana et al., 1991). A substantial proportion is inactivated by proteolytic cleavage before, or shortly after, release from trophoblast (Cole et al., 1993). Pooled hCG also contains several variants that differ in their glycosylation. An incompletely glycosylated variant of hCG is responsible for the enhanced thyrotropic activity of hCG produced by hydatidiform moles (Pekary et al., 1993). This variant is one of the principal forms of hCG in the first trimester placenta (Wang et al., 1988). Genes for allocrine hormones and genes that modify their actions are prime candidates for imprinted loci.

Chorionic Gonadotropins in Other Species

Chorionic gonadotropins (CGs) appear to have evolved independently at least three times among mammals: in primates (Tullner, 1974), equids (Murphy and Martinuk, 1991; Steger et al., 1991), and guinea pigs (Bambra et al., 1984). This section will discuss the CGs of equids because the CG of guinea pigs is poorly known. A single gene encodes the β subunits of equine luteinizing hormone (eLH) and equine chorionic gonadotropin (eCG) (Sherman et al., 1992). Therefore, unlike hLH and hCG, eLH and eCG are essentially the same hormone expressed in different tissues. An obstacle to the evolution of chorionic gonadotropins may be the requirement for the simultaneous placental expression of both α and β subunits before a functional hormone can be produced.

The latter stages of equine pregnancy are maintained by placental progesterone. Unlike humans, equids produce secondary corpora lutea during pregnancy, which contribute to the supply of ovarian progesterone that is essential for the early stages of pregnancy (Stewart and Allen, 1981; Murphy and Martinuk, 1991). Given such a mechanism, and the high levels of spontaneous abortion in horses (Chevalier-Clément, 1989), equine fetuses would gain an advantage if their CG promoted the growth and development of follicles, as well as stimulating the secretion of progesterone by established corpora lutea. Significantly, the chorionic gonadotropin/luteinizing hormone of horses (eCG/LH) has follicle-stimulating activity in pigs, rats and donkeys, but not in horses (Stewart and Allen, 1981; Guillou and Combarnous, 1983). Such a situation would arise if eCG/LH β subunits were selected to have increased affinity for the FSH-receptor because this reduced the rate of miscarriage,

and FSH-receptors were subsequently selected to discriminate against eCG/LH to avoid manipulation.

Donkey CG has little or no FSH activity (Murphy and Martinuk, 1991). Therefore, the follicle-stimulating activity of eCG/LH has probably arisen subsequent to the divergence of horses and donkeys. If so, the FSH-receptors of donkey ovaries have not been selected to discriminate against eCG/LH. This has dramatic effects in matings between male horses and female donkeys (hinny pregnancies). The CG/LH produced by the hinny conceptus stimulates massive follicular growth. As a result, progesterone levels in maternal blood are elevated twentyfold above normal. In the reciprocal cross (mule pregnancies), donkey CG/LH has no such effect on the mare's ovaries, and progesterone levels are normal (Stewart and Allen, 1981).

Chorionic gonadotropins of equids and primates may initially have evolved because they caused a shift in power towards offspring. That is, some fetuses survived that would otherwise have miscarried because they carried a gene for the CG. Mothers, however, may ultimately have benefited because they were able to reduce their own production of LH, evolve new mechanisms of adaptive miscarriage, and use CG as a measure of embryo quality. Embryos now had to produce CG and reveal their presence in early pregnancy, with an overall gain in the information available to mothers.

Nausea and Vomiting of Pregnancy

Most women experience some degree of nausea, with or without vomiting, during the first trimester of pregnancy (Fairweather, 1968; Järnfelt-Samsioe, 1987; O'Brien and Newton, 1989). In this section, I discuss various hypotheses that have been proposed to account for nausea during pregnancy, but I am unable to come to clear conclusions because the evidence remains equivocal. Nausea and vomiting are particularly common in pregnancies with large placental masses, such as twin gestations or when the conceptus is a hydatidiform mole. This suggests that a placental factor is responsible for nausea (Fairweather, 1968). hCG has been a prime suspect because its concentration is highest when symptoms are most severe, and declines as symptoms disappear (Schoenek, 1942; and many other authors). On the other hand, choriocarcinomas release large quantities of hCG, but are not associated with nausea and vomiting (Järnfelt-Samsioe, 1987). Comparisons among women in their first trimester have either found (Masson et al., 1985; Mori et al., 1988; Goodwin, Montoro, Mestman, Pekary, and Hershman, 1992) or failed to find (Fairweather, 1968; Soules et al., 1980) a correlation between hCG levels and the incidence or severity of symptoms. A variant of this hypothesis would be that nausea is caused by some component of heterogenous hCG.

Other authors have suggested that rising levels of estradiol are responsible for the nausea of early pregnancy (Depue et al., 1987; Järnfelt-Samsioe, 1987). In support of this hypothesis, exogenous estrogens cause nausea in some men and women, and women who are intolerant of oral contraceptives have a higher incidence of vomiting when pregnant (Järnfelt-Samsioe et al., 1983, 1985). Estradiol concentrations, however, continue to rise after symptoms have abated (Buster and Simon, 1989), so a subsidiary hypothesis is necessary to explain why nausea is restricted to the first trimester. As was the case with hCG, different studies have found (Depue et al., 1987) or failed to find (Masson et al., 1985), a correlation between severity of symptoms and estradiol levels.

A third hypothesis is that maternal nausea is caused by the transient hyperthyroidism observed in some pregnancies. Some studies have found that vomiting is associated with elevated thyroid hormones (Jeffcoate and Bain, 1985; Mori et al., 1988; Goodwin, Montoro, and Mestman, 1992), but other studies did not (Evans et al., 1986; Wilson et al., 1992). Vomiting is an occasional symptom of thyrotoxicosis in nonpregnant women (Rosenthal et al., 1976), but a common symptom of pregnancy. Elevated thyroid hormones and hCG are not mutually exclusive explanations of nausea, because hCG may be the thyrotropic factor of early pregnancy (Goodwin, Montoro, Mestman, Pekary, and Hershman, 1992; Pekary et al., 1993). Scenarios could also be imagined in which estradiol, hCG, and thyroid hormones all interact. If nausea is a con-

sequence of the hormonal milieu of early pregnancy, it may be misleading to look for a single factor.

Another unresolved issue is whether maternal nausea is a side effect of high levels of placental hormones and without adaptive function, or whether nausea confers benefits on maternal genes, fetal genes, or both. Profet (1988, 1992) has proposed that nausea has evolved to minimize maternal ingestion of dietary teratogens, because nausea occurs during early pregnancy when the risks of teratogenesis are greatest but when the nutritional demands of the embryo are small. In her view, pregnancy sickness probably arose by the recalibration of existing maternal mechanisms that induced nausea and vomiting in response to toxins. Conflict would be possible if mother and embryo favor different thresholds for vomiting (Profet, 1992).

Several studies have found that women who suffer from nausea and vomiting are less likely to miscarry during first trimester than are asymptomatic women (see M. M. Weigel and R. M. Weigel, 1989; R. M. Weigel and M. M. Weigel, 1989). This observation is compatible with increased teratogenesis and miscarriage in the absence of nausea (Profet, 1992), with nausea being a side effect of fetal attempts to avoid miscarriage, or with nausea and fetal vigor being correlated and mothers aborting less vigorous fetuses. The unresolved questions about "morning sickness" require a better understanding of biochemical mechanisms.

Fuel Supplies

The regulation of maternal blood glucose is altered during pregnancy. Fasting blood sugar falls during early pregnancy, but stabilizes after week 12 and is maintained at this new lower level until delivery. The metabolic demands of the fetus cannot account for lower glucose levels, because fetal demands are small during early pregnancy when maternal blood sugar is falling, but increase rapidly in later pregnancy when maternal blood sugar is stable. Thus, the mother appears to reset her homeostatic controls at a lower level during pregnancy (Lind and Aspillaga, 1988). By contrast to glucose, fasting insulin remains close to nonpregnant levels during the first and second trimester, but then increases during the third trimester in parallel with growth of the fetus. In the nonpregnant state, blood glucose rises after a carbohydrate meal, but rapidly returns to fasting levels in response to insulin. After a similar meal in late pregnancy, maternal blood glucose and insulin both reach higher peaks and remain elevated for longer periods. The same glucose challenge causes an exaggerated insulin response, but the response is less effective at reducing blood sugar (Ryan et al., 1985; Buchanan et al., 1990; Catalano et al., 1991; Kühl, 1991).

Two features of carbohydrate metabolism during pregnancy are puzzling from a nonconflict perspective: Why should a mother restrict fetal access to glucose, and why should she increase her production of insulin at the same time as she is becoming resistant to its effects? The second question is puzzling because increased resistance and increased production tend to cancel and it would seemingly be more efficient to achieve the same result with less resistance and lower production.

The theory of genetic conflict suggests answers to both questions. First, if fetal demands went unopposed, the fetus would remove more glucose from maternal blood than is in maternal interests. The glucose transport system of the syncytiotrophoblast has excess capacity, so that placental uptake is roughly proportional to maternal glucose levels, even at supranormal concentrations (Johnson and Smith, 1980, 1985; Hauguel et al., 1986). The conflict hypothesis predicts that the mother reduces her blood sugar to limit fetal uptake. Second, a mother and her fetus will compete after every meal over the share that each receives. The longer the mother takes to reduce her blood sugar, the greater the share taken by the fetus. The conflict hypothesis predicts that the insulin resistance of late pregnancy is caused by placental allocrine hormones and that the increased production of insulin is a maternal countermeasure.

Patients with abnormally high levels of human growth hormone (hGH) are resistant to the effects of insulin. For this reason, Daughaday and Kipnis (1966) suggested that human placental lactogen (hPL), a GH-related placental hormone, was the diabetogenic factor of pregnancy. This hypothesis was supported

by experimental studies in which hPL increased insulin resistance in nonpregnant subjects (Beck and Daughaday, 1967; Grumbach et al., 1968; Samaan et al., 1968). In addition to hPL, the placenta also releases human placental growth hormone (hPGH), another GH-related hormone. hGH, hPL, and hPGH are encoded at 17q22-q24, in a cluster of five genes that have evolved by a series of duplications from an ancestral growth hormone gene. Of the five genes, *hGH-N* encodes hGH; *hCS-A* and *hCS-B* encode hPL; *hGH-V* encodes hPGH; and *hCS-L* is a pseudogene. The mature products of *hCS-A* and *hCS-B* have identical amino acid sequences because of a recent gene conversion (Chen et al., 1989; Walker et al., 1991).

As discussed in a previous section, the manipulation of maternal responses by allocrine hormones is predicted to favor an evolutionary escalation in which increased maternal resistance to manipulation favors increased placental production of the hormone. hPL (and to a lesser extent hPGH) matches these predictions. hPL is the most abundant peptide hormone produced by primates. Its concentration in maternal serum increases throughout pregnancy, reaching 5 to 15 μg/ml near term, at which stage syncytiotrophoblast secretes 1 to 3 g/day. Levels of hPGH are much lower, but follow a similar temporal pattern, exceeding 15 ng/ml near term. Concentrations of hPL and hPGH in fetal serum are much lower than concentrations in maternal serum (Frankenne et al., 1988; Eriksson et al., 1989; Walker et al., 1991). For comparison, the plasma concentration of hGH, integrated over a day, is about 3 to 6 ng/ml in young nonpregnant adults (Daughaday, 1989).

Despite their high concentrations, neither hPL nor hPGH is essential for a successful outcome of pregnancy. Birthweight (and lactation) have been within the normal range in pregnancies with a complete absence of hPL (Simon et al., 1986; Parks, 1989), and an uneventful gestation has been reported for a child with homozygous deletions of *hCS-A*, *hCS-B*, and *hGH-V* (Wurzel et al., 1982). The combination of very high production with minimal effects is consistent with an interpretation of allocrine conflict. The conflict hypothesis does predict that fetuses should gain a marginal benefit from hPL production, at least under some circumstances. A positive correlation has been observed between birthweight and hPL concentration in maternal serum during the third trimester (Howell et al., 1985), but this could reflect either a direct effect of hPL or an indirect correlation with placental weight.

Placental secretion of hPL appears to be largely independent of maternal regulation (Walker et al., 1991). The concentration of hPL in maternal serum does not respond to fluctuations in the glucose or amino acid content of maternal blood (Kühl et al., 1975; Artenisio et al., 1980), although some evidence suggests that the placenta increases its output of hPL in response to prolonged maternal fasting (Kim and Felig, 1971; Tyson et al., 1971, 1976). The absence of direct maternal regulation is another prediction of the conflict hypothesis.

Primate growth hormones, such as hGH, bind to prolactin receptors as well as GH receptors (Cunningham and Wells, 1991). By contrast, hPL has little affinity for the GH receptor but retains strong affinity for the prolactin receptor (Lowman et al., 1991) despite 87 percent amino acid identity with hGH. Molecular studies have shown that hGH and hPL differ at precisely those amino acid positions that determine hGH's affinity for the GH receptor (Cunningham and Wells, 1991; Lowman et al., 1991). These substitutions appear to have been actively selected because the rate of replacement changes (for the entire coding sequence) is similar to the rate of silent substitutions (Talmadge et al., 1984). The gene conversion event, which was responsible for the close similarity of *hCS-A* and *hCS-B*, probably spread to fixation because it transferred substitutions that were adaptive for the fetus from one gene to the other.

The conflict hypothesis proposes that hPL subverts normal maternal responses to hGH via the prolactin receptor, so as to increase the supply of nutrients to the fetus, and that effects through the prolactin receptor had to be decoupled from effects through the GH receptor before placental production of hPL could escalate to its present high level. Therefore, to understand the maternal targets of fetal manipulation, we must understand the

normal effects of hGH in the nonpregnant state.

At present there is little direct evidence about which of hGH's effects are mediated through which receptor. The Laron syndrome is caused by defects in the GH receptor and is associated with high levels of hGH, low levels of IGF-I, and severe postnatal growth retardation (Elders et al., 1973; Godowski et al., 1989; Duquesnoy et al., 1991). Thus, the effects of hGH on linear growth appear to be mediated primarily through the GH receptor, consistent with results from other species.

hGH also has metabolic effects (Davidson, 1987). In the nonpregnant state, the release of hGH counters low blood sugar by augmenting glucose production, decreasing glucose utilization, and accelerating lipolysis (De Feo et al., 1989). In addition, hGH causes tissues to become resistant to the effects of insulin by a postreceptor mechanism (Rizza et al., 1982). The overall effect is a shift from using glucose to using fat as the principal energy source, thus reducing gluconeogenesis and conserving protein. Serum levels of hGH are particularly high in anorexia nervosa (Counts et al., 1992) and in malnourished children (Soliman et al., 1986). The conservation of amino acids would be adaptive during starvation as well as during linear growth.

Many of the metabolic effects of hGH are probably mediated through the prolactin receptor. The best evidence comes from the known effects of hPL and prolactin, hormones that bind to the prolactin receptor but not to the GH receptor. hPL enhances lipolysis and increases insulin resistance when administered to nonpregnant subjects (Grumbach et al., 1966; Samaan et al., 1968), prolactin-producing tumors are associated with increased resistance to the effects of insulin (Landgraf et al., 1977), and hyperprolactinemia mimics the metabolic changes of late pregnancy (Gustafson et al., 1980). Therefore, the insulin-antagonistic effects of hGH are probably also mediated through the prolactin receptor, and it is these processes that are the likely target of hPL's actions. As I have argued above, the fetus should benefit from increased insulin resistance of maternal tissues because this increases fetal access to nutrients after maternal meals. Nonprimate growth hormones do not bind to prolactin receptors (Kelly et al., 1991). Significantly, the placental lactogens of rodents and ruminants have been derived from duplications of the prolactin gene (Jackson-Grusby et al., 1988; Dietz et al., 1992). Thus maternal and fetal genes appear to be in conflict over control of maternal prolactin receptors in rodents and ruminants as well as in primates.

Unlike hPL, hPGH binds strongly to GH receptors as well as prolactin receptors (Baumann et al., 1991; MacLeod et al., 1991). In the nonpregnant state, stimulation of hepatic GH receptors promotes the release of IGF-I, which in turn inhibits the release of hGH from the pituitary. hPGH is not subject to this negative feedback and has been implicated in the rise in maternal IGF-I that occurs toward term (Caufriez et al., 1990). High levels of IGF-I are suspected of being responsible for the coarsening of facial features that sometimes occurs during pregnancy (Baumann et al., 1991). By the end of pregnancy, the maternal pituitary has ceased to release hGH, and hPGH is the predominant GH in maternal serum (Eriksson et al., 1989; Caufriez et al., 1990). At present, it is unclear whether fetal genes gain any benefit from the binding of hPGH to maternal GH receptors, or whether fetal benefits are gained solely through prolactin receptors, with effects through GH receptors an unwanted side effect.

The nutrient content of maternal blood will be determined by the balance between allocrine manipulation and maternal countermeasures. Pregnant women occupy a continuum with respect to their ability to reduce blood sugar after a meal. At one extreme, glucose levels remain elevated for long periods and a woman is described as having glucose intolerance or gestational diabetes. However, the choice of a boundary between normal and abnormal glucose tolerance appears arbitrary in biological terms (Farmer et al., 1992). Glucose intolerance develops when a woman is unable to increase her insulin production sufficiently to match the peripheral insulin resistance of pregnancy (Kühl, 1991). On average, pregnant women with "poor" glucose tolerance have a relatively low insulin response to a glucose challenge (Farmer et al., 1992). In a study of nondiabetic pregnant women,

birthweight was positively correlated with maternal glucose levels two hours after a glucose meal (Tallarigo et al., 1986). The benefit of increased maternal glucose levels for the fetus may be gained at some cost to its mother's health. Women who experience impaired glucose tolerance during pregnancy have an increased risk of developing overt diabetes in later life (Dornhorst et al., 1990; Damm et al., 1992).

Pancreatic islet cells become hypertrophied during pregnancy (Rosenloecher, 1932; Van Assche et al., 1978), probably as a direct response to high levels of hPL (Billestrup and Nielsen, 1991; Brelje et al., 1993). Fetal genes may have been selected to counter the increased maternal output of insulin. The placenta contains enzymes that rapidly degrade insulin (Buse et al., 1962; Steel et al., 1979; Lai et al., 1985) and, thus, may act as a sink for maternal insulin. Any effect must be minor because insulin's half-life is little changed during pregnancy (Lind et al., 1977). Challier et al. (1986) have calculated that the placenta removes 25% of the insulin entering the intervillous space, but that this increases the metabolic clearance of insulin by only 10%.

Syncytiotrophoblast expresses numerous insulin receptors at its maternal face (Nelson et al., 1978; Whitsett et al., 1979). Their density increases from the first to the third trimester (Lai et al., 1985). At present, no unambiguous function has been demonstrated for placental insulin receptors. Placental glucose metabolism and glucose transport are insensitive to variation in maternal insulin (Challier et al., 1986), as is placental uptake of amino acids (Steel et al., 1979). The possibility that insulin receptors function as a sink for maternal insulin has not been considered. If placental receptors have a signaling function, the conflict hypothesis predicts that such signals would initiate placental responses that counter the effects of maternal insulin secretion.

Affluent mothers usually have sufficient food to meet all their own needs and fetal needs. This is not true for all women today nor for all women during human evolution. Therefore, maternal-fetal relations have evolved in the context of unpredictable food shortages. Overt conflict should be most apparent in times of nutritional stress, but conflict is also expected in times of plenty because resources transferred to a fetus cannot be recalled if conditions worsen. This section has discussed conflict over glucose levels in maternal blood, but similar conflicts would be expected over minerals and other nutrients if these are in short supply. The next section addresses conflicts over the quantity, rather than the quality, of blood reaching the intervillous space.

PUTTING UP RESISTANCE

Hemodynamics of Pregnancy

The vascular resistance between two points is defined as the pressure difference between the points divided by the flow rate. For example, total systemic resistance is calculated by dividing the mean arterial pressure by cardiac output. Mean arterial pressure is implicitly a pressure difference because venous pressure is low. Thus blood pressure can be viewed as the outcome of a relation between a property of the vasculature (resistance) and a property of the pump (cardiac output, flow rate). Arterial pressure will increase if either cardiac output or systemic resistance increases and the other remains unchanged. A constant pressure can be maintained if increases in output are compensated by appropriate decreases in resistance. For streamline flow in a rigid cylindrical tube, resistance is proportional to $L\eta/r^4$, where L and r are the length and radius of the tube, and η is the viscosity of the fluid (Folkow and Neil, 1971). This relation (Poiseuille's Law) illustrates the dramatic effect of small changes in the radius on a vessel's resistance to flow.

During pregnancy, fetal needs are supplied from a mother's systemic circulation. Blood leaves the maternal left ventricle via the aorta, is distributed to the various parts of the body (including the placenta), and returns to the right atrium via the superior and inferior venae cavae. Different organs are supplied by different subcirculations, arranged in parallel. The pressure difference between the aorta and venae cavae is common to all subcirculations, so the proportion of total output that reaches each organ is determined by the relative resistance of its subcirculation. Most of the total systemic resistance resides in the arterioles and small arteries, and the distribution

of blood among organs is largely determined by variation in the radius of these vessels (Folkow and Neil, 1971).

For simplicity, a mother's systemic circulation can be considered to consist of two parallel subcirculations: the uteroplacental circulation, from which the fetus gains its nutrients, and the nonplacental remainder. Maternal and fetal genes will come into conflict over the relative flow to each subcirculation. In theory, the fetus can increase its share of cardiac output by decreasing resistance in the uteroplacental circulation or by increasing resistance in the nonplacental circulation, and the mother can reduce the fetal share by the opposite actions. The implication for the fetus of a change in total systemic resistance is ambiguous because the change could reside in the uteroplacental or the nonplacental resistance, but the two possibilities have opposite consequences for fetal nutrition.

Fetal cells reduce uteroplacental resistance by their invasion of maternal vessels. The spiral arteries are transformed by trophoblast into wide-bored, low-resistance channels that cannot constrict (Brosens et al., 1967; Pijnenborg, 1990), and arterial blood empties into the large intervillous space, rather than being constrained to a capillary bed. As a consequence, almost all the resistance in the uteroplacental circulation occurs before blood reaches the transformed segments of the spiral arteries (W. Moll, Künzel, and Herberger, 1974). An index of uteroplacental resistance can be obtained by Doppler ultrasound. Resistance falls until 24 weeks gestation (when invasion of the arteries is complete), with little change thereafter (McParland and Pearce, 1988; Pearce et al., 1988). The contrast between epitheliochorial and hemochorial placentation is illuminating. Maternal vessels remain intact in the epitheliochorial placenta of sheep and the major resistance to flow occurs once maternal blood reaches the placenta, whereas, in the hemochorial placentas of monkeys, guinea pigs, rats, and rabbits, the major resistance occurs before blood reaches the placenta (W. Moll and Künzel, 1973; W. Moll, Künzel, and Herberger, 1974; W. Moll, Künzel, Stolte, Kleinhout, de Jong, and Veth, 1974).

Fetal efforts to enhance the uteroplacental blood supply are opposed by maternal tissues. The decidual reaction is most pronounced, and occurs earliest, around the spiral arteries (Ferenczy, 1987; Waites et al., 1988). The coils of the spiral arteries may themselves be a maternal countermeasure, because the resistance of a vessel is proportional to its length and curved vessels have greater resistance than straight vessels of the same dimensions (Caro et al., 1978). The spiral arteries lengthen and become more convoluted during the early stages of pregnancy, at least in rhesus macaques (Ramsey, 1949). It has long been recognized that the "curling arteries" reduce blood flow to the placenta (Hunter, 1786). If I understand the conventional viewpoint correctly, the arterial coils have been seen as a maternal adaptation to protect the delicate embryo from high arterial pressures. The spirals could uncoil to accommodate expansion of the uterus, but this does not appear to be an important function in humans (Ramsey, 1949).

After transformation of the spiral arteries, the systemic circulation contains a low-resistance subcircuit that is not subject to maternal vasoregulation. As a result, flow through the intervillous space will be largely determined by the pressure in the major maternal arteries. *For any given resistance of the uteroplacental circulation, fetal nutrition will be enhanced by an increase in mean arterial pressure.* Therefore, the conflict hypothesis predicts that placental factors will act to increase maternal blood pressure and maternal factors will act to reduce blood pressure.

Maternal blood pressure falls below nonpregnant levels in the first trimester, reaches a nadir in midpregnancy then, during the second half of pregnancy, rises above nonpregnant levels in some women but remains low in others (MacGillivray et al., 1969; Reiss et al., 1987; Redman, 1989a; Easterling et al., 1990). Vascular resistance must decline in the first trimester and increase in the third trimester because cardiac output rises during early pregnancy when arterial pressure is falling (Lees et al., 1967; Katz et al., 1978), but shows little change after 27 weeks when arterial pressure is rising (Easterling et al., 1990). Resistance in the forearm was half nonpregnant values in one group of pregnant women (Sowers et al., 1990), and similar observations have been reported by others (Spetz, 1964; Gins-

burg and Duncan, 1967). Pregnant women maintain vasodilation of their extremities under cool conditions (Burt, 1949). The decreased tone of vascular smooth muscle is expressed as increased venous distensibility and an increased risk of varicose veins (McCausland et al., 1961).

The increase in cardiac output exceeds maternal metabolic demands until late in pregnancy (Lees et al., 1967), at least as measured by a reduced oxygen difference between arterial and venous blood (Bader et al., 1955). If the function of increased output is to supply fetal demands, the same increase in blood supply to the placenta could be achieved by a smaller increase in output and a smaller decrease in nonplacental resistance. Thus the degree of vasodilation is puzzling from a nonconflict perspective. The conflict hypothesis suggests that mothers reduce vascular resistance during early pregnancy to ration fetal nutrients, and that the subsequent increase in vascular resistance represents the changing "balance of power" as the fetus grows larger. A corollary is that placental factors contribute to the increase in maternal cardiac output.

At first sight, the fetus has limited ability to increase its share of cardiac output by increasing nonplacental resistance because blood from the placenta must first pass through the right side of the heart and the pulmonary circulation before returning to the systemic circulation. Maternal blood is well mixed in the process and placental factors cannot be specifically targeted to the nonplacental circulation. Placental factors, however, have an opportunity to preferentially increase nonplacental resistance because the uteroplacental arteries are highly modified and unresponsive to vasoconstrictors.

Pregnancy-Induced Hypertension

The claim that fetuses benefit from increases in maternal blood pressure may surprise some readers because high blood pressure during pregnancy can be associated with life-threatening crises for mother and child, particularly when hypertension is accompanied by excessive protein in maternal urine (proteinuria). For this reason a distinction should be made between hypertension without proteinuria (gestational hypertension) and hypertension with proteinuria (preeclampsia). Maternal blood pressures form a continuum, so that the dividing line between normotensive and hypertensive pregnancies is arbitrary (Redman, 1989a). The conflict hypothesis predicts that a mother's position on the continuum is determined by the balance between fetal factors increasing blood pressure and maternal factors decreasing blood pressure. There is currently no consensus about what determines maternal blood pressure during pregnancy, but the simultaneous elevation of vasoconstrictors (Baker et al., 1990) and vasodilators (Cusson et al., 1985; Milsom et al., 1988) is suggestive of conflict.

Gestational hypertension has a good fetal prognosis. In a large British study, hypertensive pregnancies, had lower perinatal mortality than normotensive pregnancies, even when the proteinuric subset was included (Symonds, 1980). Among white American women, birthweight was positively correlated with maternal blood pressure for mothers with low prepregnancy weight and low weight gain during pregnancy (Naeye, 1981a,b). As further evidence of a relationship between maternal blood pressure and fetal growth, chronic hypertension (existing before pregnancy) is associated with high birthweight (Salafia et al., 1990) and chronic hypotension with low birthweight (Grünberger et al., 1979; Ng and Walters, 1992).

Preeclampsia is a major cause of maternal and fetal morbidity and mortality. Maternal complications include convulsions, cerebral hemorrhage, cardiac arrest, retinal detachment, hepatic rupture, kidney failure, and coagulation disorders (Redman, 1989b). Infants of preeclamptic pregnancies have increased risks of prematurity, stillbirth, perinatal mortality, and intrauterine growth retardation (Page and Christianson, 1976; Naeye and Friedman, 1979; Symonds, 1980). The maternal spiral arteries are poorly modified by trophoblast in many preeclamptic pregnancies (Gerretsen et al., 1983; Khong et al., 1986; Robertson et al., 1986; Pijnenborg et al., 1991). Therefore, poor fetal growth is probably antecedent to preeclampsia because preeclampsia usually develops in the third trimester after the invasion of the spiral arteries is complete. The idea that the clinical symptoms

of preeclampsia are often a sequel to poor placental perfusion seems to have gained general acceptance (Friedman et al., 1991; Redman, 1991).

Preeclampsia is principally a disease of first pregnancies (MacGillivray, 1958). A plausible explanation is that the spiral arteries never fully recover from a first pregnancy and thus offer less resistance to flow in subsequent pregnancies. Consistent with this hypothesis, average birthweight increases with parity (Karn and Penrose, 1951; Camilleri and Cremona, 1970), and pathologists can tell whether a woman has ever given birth by observing changes to the walls of uterine vessels (Pankow, 1906). Preeclampsia is particularly common in pregnancies with large placental masses, including pregnancies with a hydatidiform mole in which there is excessive proliferation of trophoblast without associated fetal tissues (T. N. A. Jeffcoate, 1966; Redman, 1991). Significantly, hydatidiform moles have two paternal genomes but no maternal genome (Wake et al., 1978).

Recent reviews suggest that hypertension in untreated preeclampsia results from increased systemic resistance rather than increased cardiac output (Wallenburg, 1988; Sibai and Mabie, 1991). The placenta is believed to release cytotoxic factors that damage the endothelium of maternal vessels (Rodgers et al., 1988; J. M. Roberts et al., 1989; Tsukimori et al., 1992), causing arterioles to constrict and increasing systemic resistance. Proteinuria is the result of serum proteins leaking from damaged glomeruli into renal tubules (Studd, 1973) and may be one expression of generalized endothelial damage. Fibrin deposition is increased during normal pregnancy (Fletcher et al., 1979; McKay, 1981) and the effect is accentuated in preeclampsia (Socol et al., 1985; de Boer et al., 1989), possibly in response to endothelial damage (Ballegeer et al., 1992). Fibrin deposits in the smaller maternal vessels would further increase resistance.

Small increments in the birthweight of semistarved fetuses may often have caused major increases in subsequent survival despite substantial costs to mothers. Therefore, endothelial damage may have evolved as a high-risk fetal strategy to increase nonplacental resistance when a fetus's uteroplacental blood supply is inadequate. Page (1939) expressed a similar hypothesis about the origins of preeclampsia. "To revert for a moment to teleologic reasoning," he wrote, "if the placenta . . . should be unable to obtain a sufficient maternal circulation for its demands, it might be capable of increasing this supply by raising the systemic blood pressure" (p. 292). In this memorable passage, Page described the placenta as "a ruthless parasitic organ existing solely for the maintenance and protection of the fetus, perhaps too often to the disregard of the maternal organism."

The conflict hypothesis has important implications for the way that preeclampsia is interpreted. First, fetal actions need to be clearly distinguished from maternal responses. Second, the placental factors responsible for preeclamptic symptoms may be a stereotyped response to poor placental perfusion, whereas the causes of poor perfusion may be diverse. Fetal actions in preeclampsia should be seen as evidence of normal, rather than aberrant, placental function. Third, preeclamptic symptoms may not be caused by a single placental factor because the fetus may target multiple maternal systems once it becomes committed to raising blood pressure by drastic action. Fourth, conflicts may exist between the maternal and paternal genomes of the fetus. Susceptibility to preeclampsia has a clear familial component but a satisfactory genetic model has remained elusive (Cooper et al., 1993). The possibility of genetic imprinting or gestational drive should be considered in future investigations.

BIRTH AND BEYOND

Genetic conflicts undoubtedly continue after birth, but parturition marks an important transition because fetal genes lose their ability to directly manipulate maternal responses by biochemical means. Parturition itself has considerable risks for both mother and infant. At birth, the fetal cranium is close to the maximum size that can be delivered through the maternal pelvic outlet. An important evolutionary question is why the fetus waits so long before it is born. I suspect that fetuses attempt to remain in the womb until the nutritional benefits of remaining inside are not worth the

increasing risks of delivery. Over evolutionary time, the duration of pregnancy is possibly determined by a conflict between fetal genes favoring slightly longer gestations and maternal genes favoring slightly shorter gestations. This question deserves further study.

Trivers (1974) proposed that postnatal conflict between parents and offspring would primarily be mediated by behavioral acts, in contrast to prenatal conflict, which would primarily be mediated by chemical acts. This view is undoubtedly correct (assuming a meaningful distinction can be made between behavioral and chemical acts), but biochemical conflict is possible after birth, because the maternal and paternal genomes of the child remain in conflict with respect to the costs they are prepared to impose on the child's mother. Conflict could be expressed within a child's nervous system over the activation threshold for particular behaviors. Moreover, the outcome of the struggle between maternal and paternal genes within the child could be influenced by factors in the mother's milk. Human milk contains benzodiazepinelike substances (Dencker et al., 1992). GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter of the central nervous system, and benzodiazepines (e.g., Valium) modulate the activity of $GABA_A$ receptors (Olsen and Tobin, 1990). If the child's responses through $GABA_A$ receptors are the target of natural sedatives in milk, the child's paternally derived receptors could be selected to be unresponsive (or unexpressed) in those classes of neurons that determine behaviors costly to the mother.

Evidence that maternal and paternal genes may play different roles within a child's nervous system is provided by Prader-Willi and Angelman syndromes. Prader-Willi syndrome (PWS) is caused by the presence of a maternal copy of 15q11–13 without a paternal copy, whereas Angelman syndrome (AS) is caused by the presence of a paternal copy without a maternal copy (Nicholls et al., 1992). Paternal deletions (PWS) are associated with a poor suckling response (usually requiring gastric feeding), a weak cry, physical inactivity, and sleepiness (Butler, 1990). Maternal deletions (AS) are also associated with suckling difficulties, but in this case suckling is prolonged but poorly coordinated. By contrast to PWS, Angelman children are highly active when awake and have sleeping difficulties with frequent waking (Magenis et al., 1990; Clayton-Smith, 1992). In normal development, paternal genes in this region would appear to promote greater activity whereas maternal genes would appear to have a restraining influence.

Prader-Willi children become obese in their first or second year, with an insatiable appetite that is probably a response to physiological starvation caused by the inappropriate deposition of fat. Obesity is accompanied by reduced muscular and skeletal growth (Butler, 1990; Butler et al., 1991). This phenotype suggests that there may be maternal-paternal conflict in normal development over the metabolic allocation of resources among different functions. Maternally derived genes might favor greater relative allocation to energy reserves if this reduced the maternal cost of supporting the child in the event of famine.

One of the genes located in the PWS/AS region encodes the small nuclear ribonucleoprotein peptide N, a splicing factor of unknown function that is expressed in the brain. This gene is imprinted in the mouse (Leff et al., 1992). The region also contains genes for the α_5 and β_3 subunits of the $GABA_A$ receptor (Wagstaff et al., 1991; Sinnett et al., 1993). Whether any of these genes are imprinted in humans is presently unknown. GABA appears to have a regulatory role in the endocrine pancreas (Sorensen et al., 1991) and inhibits the release of somatostatin, a negative regulator of GH, from the hypothalamus (Rage et al., 1992). These diverse effects of GABA suggest one way in which the metabolic, growth and neurological features of PWS and AS might be related.

CODA

Human placentation has been shaped by a tangled interplay of selective forces. Conflict arises because fetal genes will increase in frequency if they cause their fetus to take a little bit more than maternal genes are selected to give. Conflict, however, is tempered by accommodation. Other genes will increase in frequency if they ensure the same benefit to the fetus while reducing the cost to the mother, independent of whether the gene is expressed in mother or fetus. Most previous discussions

have emphasized the common interests of maternal and fetal genes, whereas this article has emphasized aspects of conflict.

The medical complications of pregnancy and childbirth have usually been seen as failures of adaptation, as an expression of developmental constraints from our remote ancestry, but the existence of genetic conflicts offers another explanation. Relations between a mother and her fetus are not subject to the intricate homeostatic mechanisms that are characteristic of interactions between different tissues of the same body because messages cannot be trusted. Both parties often have an incentive to send misleading information. If a mother signaled to her fetus to reduce its demands because of a present danger to the mother's survival, fetal genes that responded would be vulnerable to exploitation by maternal genes that sent the same message when there was no danger. Similarly, maternal and fetal genes would both benefit if a given transfer of resources was achieved with a lesser production of allocrine hormones and less maternal resistance, but such an agreement is evolutionarily unenforceable.

The failure to recognize genetic conflicts has contributed to the placenta occupying a peripheral and problematic position within evolutionary biology. Turner (1876a) discussed the diversity of mammalian placentation in relation to the new theory of evolution by natural selection. "There can be little doubt that organisms may become modified by the direct action of surrounding agencies. . ." (p. 41), he wrote, "but the conditions generally under which the placenta is placed in all mammals seem to be so nearly uniform, that it is difficult to see how it can be affected by surrounding agencies" (p. 42). Turner tried to relate placental type to other attributes of an organism such as speed, gestation length, adult size, uterine shape, and litter size, but could find no characters that grouped together lemurs, mares, whales, and pigs (with "diffuse" [≈ epitheliochorial] placentas) on the one hand and hares, hedgehogs, moles, and humans (with "discoid" [≈ hemochorial] placentas) on the other.

Grosser (1933) believed that the special characters of the human placenta could not have been attained by adaptation, but had evolved by a process of orthogenesis. He noted that the human placenta was arguably less efficient than the simple epitheliochorial placenta of the cow, because although the bovine placenta had a comparable absorptive surface, it was able to support the growth of a much larger fetus within the same duration of pregnancy. Grosser predicted disastrous consequences from the human placenta's continued growth and specialization. "It is curious to visualise the earth full of life, the sun shining over sea and land, but humanity extinct, having disappeared through the operation of internal factors, like other conspicuous and mighty species of former times, curious ruins alone remaining of what had once been the master of the world" (p. 1058).

Mossman (1991) concluded, "The more I consider the evidence, the more convinced I become that the membranes are more reliable than adult characters of the body in showing ancient affinities between higher mammalian categories such as families, suborders and orders. This is true because fetal membranes need not be adapted to the environment in which the adult lives, nor to the adult's behavioural peculiarities" (p. 2). This conviction led to the courageous proposal that lemurs be classified with horses, and sloths with the anthropoid apes (Mossman, 1937, 1987, 1991).

It is easy to smile at such ideas, but Grosser and Mossman were respected anatomists making honest attempts to explain a system that did not fit neatly within orthodox concepts of adaptation. The conflict hypothesis suggests that placental evolution is driven by internal forces that are largely independent of the external environment, that these forces result in rapid divergence among lineages, and that seemingly maladaptive features of placentation can be explained by natural selection favoring divergent outcomes for maternal and fetal genes.

ACKNOWLEDGMENTS

This paper arose from an invitation to speak at an NIH conference on Genomic Imprinting and Human Disease organized by J. G. Hall, G. N. Wilson, and F. de la Cruz. It has benefited from the comments of K. Benirschke, A. Grafen, O. Judson, D. Lieberman, N. E. Pierce, M. Profet, H. K. Reeve, R. Trivers, and M. Westoby. Special thanks are due to the library staff of Oxford

and Harvard Universities. My work was supported in the United Kingdom by an Endeavour Fellowship from the Royal Society and in the United States by a Harvard Junior Fellowship from The Society of Fellows. Publication of this paper was supported by a grant from the Arthur Lawrence Green Memorial Fund, Harvard University.

REFERENCES

Amoroso, E. C. 1952. Placentation. In A. S. Parkes (ed.), *Marshall's Physiology of Reproduction*, Vol. II, 3rd ed., pp. 127-311. Longman's, Green and Company, London.

Angel, E., J. R. Davis, and R. B. Nagle. 1985. Immunohistochemical demonstration of placental hormones in the diagnosis of uterine versus ectopic pregnancy. *Am. J. Clin. Pathol.*, 84: 705-709.

Aplin, J. D., A. K. Charlton, and S. Ayad. 1988. An immunohistochemical study of human endometrial extracellular matrix during the menstrual cycle and first trimester of pregnancy. *Cell Tissue Res.*, 253:231-240.

Arkwright, P., T. Rademacher, J. Marshall, R. Dwek, and C. Redman. 1992. Glycoprotein glycosylation and the immunosuppressive effects of human pregnancy serum. *J. Reprod. Immunol.*, 21:97-102.

Artenisio, A. C., A. Volpe, F. Ragonese, G. Maccarrone, F. Forte, and F. Consolo. 1980. Behaviour of HPL and GH plasmatic rate in pregnant women at different times of their pregnancy during dynamic tests. *Horm. Metab. Res.*, 12: 205-208.

Azuma, C., F. Saji, Y. Tokugawa, T. Kimura, T. Nobunaga, M. Takemura, T. Kameda, and O. Tanizawa. 1991. Application of gene amplification by polymerase chain reaction to genetic analysis of molar mitochondrial DNA: the detection of anuclear empty ovum as the cause of complete mole. *Gynecol. Oncol.*, 40:29-33.

Bader, R. A., M. E. Bader, D. J. Rose, and E. Braunwald. 1955. Hemodynamics at rest and during exercise in normal pregnancy as studied by cardiac catheterization. *J. Clin. Invest.*, 34:1524-1536.

Baker, P. N., F. Broughton Pipkin, and E. M. Symonds. 1990. Platelet angiotensin II binding and plasma renin concentration, plasma renin substrate and plasma angiotensin II in human pregnancy. *Clin. Sci. (Lond.)*, 79:403-408.

Ballegeer, V. C., B. Spitz, L. A. De Baene, A. F. Van Assche, M. Hidajat, and A. M. Criel. 1992. Platelet activation and vascular damage in gestational hypertension. *Am. J. Obstet. Gynecol.*, 166:629-633.

Bambra, C. S., S. S. Lynch, G. R. Foxcroft, G. Robinson, and E. C. Amoroso. 1984. Purification and characterization of guinea-pig chorionic gonadotrophin. *J. Reprod. Fertil.*, 71:227-233.

Barlow, D. P., R. Stöger, B. G. Herrmann, K. Saito, and N. Schweifer. 1991. The mouse insulin-like growth factor type-2 receptor is imprinted and closely linked to the *Tme* locus. *Nature*, 349:84-87.

Bartolomei, M. S., S. Zemel, and S. M. Tilghman. 1991. Parental imprinting of the mouse H19 gene. *Nature*, 351:153-155.

Baumann, G., N. Dávila, M. A. Shaw, J. Ray, S. A. Liebhaber, and N. E. Cooke. 1991. Binding of human growth hormone (GH)-variant placental GH to GH-binding proteins in human plasma. *J. Clin. Endocrinol. & Metab.*, 73: 1175-1179.

Beck, P., and W. H. Daughaday. 1967. Human placental lactogen: studies of its acute metabolic effects and disposition in normal men. *J. Clin. Invest.*, 46:103-110.

Beischer, N. A., R. Sivasamboo, S. Vohra, S. Silpisornkosal, and S. Reid. 1970. Placental hypertrophy in severe pregnancy anaemia. *J. Obstet. Gynaecol. Br. Commonw.*, 77:398-409.

Bell, S. C. 1989. Decidualization and insulin-like growth factor (IGF) binding protein: implications for its role in stromal cell differentiation and the decidual cell in haemochorial placentation. *Hum. Reprod. (Oxf.)*, 4:125-130.

Bell, S. C., S. R. Patel, J. A. Jackson, and G. T. Waites. 1988. Major secretory protein of human decidualized endometrium in pregnancy is an insulin-like growth factor-binding protein. *J. Endocrinol.*, 118:317-328.

Benchimol, S., A. Fuks, S. Jothy, N. Beauchemin, K. Shirota, and C. P. Stanners. 1989. Carcinoembryonic antigen, a human tumor marker, functions as an intercellular adhesion molecule. *Cell*, 57:327-334.

Benirschke, K., and P. Kaufmann. 1990. *Pathology of the Human Placenta*, 2nd ed. Springer-Verlag, New York.

Bhattacharyya, S., J. Chaudhary, and C. Das. 1992. Antibodies to hCG inhibit progesterone production from human syncytiotrophoblast cells. *Placenta*, 13:135-139.

Billestrup, N., and J. H. Nielsen. 1991. The stimulatory effect of growth hormone, prolactin, and placental lactogen on β-cell proliferation is not mediated by insulin-like growth factor-I. *Endocrinology*, 129:883-888.

Bischof, P., E. Friedli, M. Martelli, and A. Campana. 1991. Expression of extracellular matrix-degrading metalloproteinases by cultured human cytotrophoblast cells: effects of cell adhesion and immunopurification. *Am. J. Obstet. Gynecol.*, 165:1791-1801.

Bo, M., and I. Boime. 1992. Identification of the transcriptionally active genes of the chorionic gonadotropin β gene cluster in vivo. *J. Biol. Chem.*, 267:3179-3184.

Boué, J., A. Boué, and P. Lazar. 1975. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. *Teratology*, 12:11-26.

Boyd, J. D. 1959. Glycogen in early human implantation sites. *Mem. Soc. Endocrinol.*, 6:26-34.

Brannan, C. I., E. C. Dees, R. S. Ingram, and S. M. Tilghman. 1990. The product of the H19 gene may function as an RNA. *Mol. Cell. Biol.*, 10:28-36.

Brelje, T. C., D. W. Scharp, P. E. Lacy, L. Ogren, F. Talamantes, M. Robertson, H. G. Friesen, and R. L. Sorensen. 1993. Effect of homologous placental lactogens, prolactins, and growth hormones on islet B-cell division and insulin secretion in rat, mouse, and human islets: implications for placental lactogen regulation of islet function during pregnancy. *Endocrinology*, 132: 879-887.

Brosens, I., and H. G. Dixon. 1966. The anatomy of the maternal side of the placenta. *J. Obstet. Gynaecol. Br. Commonw.*, 73:357-363.

Brosens, I., W. B. Robertson, and H. G. Dixon. 1967. The physiological response of the vessels of the placental bed to normal pregnancy. *J. Pathol. Bacteriol.*, 93:569-579.

Brown, K. W., A. Gardner, J. C. Williams, M. G. Mott, A. McDermott, and N. J. Maitland. 1992. Paternal origin of 11p15 duplications in the Beckwith-Wiedemann syndrome: A new case and review of the literature. *Cancer Genet. Cytogenet.*, 58:66-70.

Brown, W. E., and J. T. Bradbury. 1947. A study of the physiologic action of human chorionic hormone. The production of pseudopregnancy in women by chorionic hormone. *Am. J. Obstet. Gynecol.*, 53:749-757.

Buchanan, T. A., B. E. Metzger, N. Freinkel, and R. N. Bergman. 1990. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am. J. Obstet. Gynecol.*, 162:1008-1014.

Bulmer, J. N., J. Smith, L. Morrison, and M. Wells. 1988. Maternal and fetal cellular relationships in the human placental basal plate. *Placenta*, 9:237-246.

Burt, C. C. 1949. Peripheral skin temperature in normal pregnancy. *Lancet*, 2:787-790.

Burtin, P., P. C. Quan, and M. C. Sabine. 1975. Nonspecific cross reacting antigen as a marker for human polymorphs, macrophages and monocytes. *Nature*, 255:714-716.

Buse, M. G., W. J. Roberts, and J. Buse. 1962. The role of the human placenta in the transfer and metabolism of insulin. *J. Clin. Invest.*, 41: 29-41.

Buster, J. E., and J. A. Simon. 1989. Placental hormones, hormonal preparation for and control of parturition, and hormonal diagnosis of pregnancy. In L. J. DeGroot (ed.), *Endocrinology*, 2nd ed., pp. 2043-2073. W. B. Saunders, Philadelphia.

Butler, M. G. 1990. Prader-Willi syndrome: current understanding of cause and diagnosis. *Am. J. Med. Genet.*, 35:319-332.

Butler, M. G., J. L. Haynes, and F. J. Meaney. 1991. Anthropometric study with emphasis on hand and foot measurements in the Prader-Willi syndrome: sex, age and chromosome effects. *Clin. Genet.*, 39:39-47.

Camilleri, A. P., and V. Cremona. 1970. The effect of parity on birthweight. *J. Obstet. Gynaecol. Br. Commonw.*, 77:146-147.

Carayon, P., G. Lefort, and B. Nisula. 1980. Interaction of human chorionic gonadotropin and human luteinizing hormone with human thyroid membranes. *Endocrinology*, 106:1907-1916.

Carayon, P., S. Amr, B. Nisula, and S. Lissitzky. 1981. Effect of carboxypeptidase digestion of the human choriogonadotropin molecule on its thyrotropic activity. *Endocrinology*, 108:1891-1898.

Caro, C. G., T. J. Pedley, R. C. Schroter, and W. A. Seed. 1978. *The Mechanics of the Circulation*. Oxford University Press, Oxford.

Catalano, P. M., E. D. Tyzbir, N. M. Roman, S. B. Amini, and E. A. H. Sims. 1991. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am. J. Obstet. Gynecol.*, 165:1667-1672.

Catalano, P. M., E. D. Tyzbir, S. R. Allen, J. H. McBean, and T. L. McAuliffe. 1992. Evaluation of fetal growth by estimation of neonatal body composition. *Obstet. Gynecol.*, 79:46-50.

Caufriez, A., F. Frankenne, Y. Englert, J. Golstein, F. Cantraine, G. Hennen, and G. Copinschi. 1990. Placental human growth hormone as a potential regulator of maternal IGF-I during human pregnancy. *Am. J. Physiol.*, 258:E1014-E1019.

Challier, J. C., S. Hauguel, and V. Desmaizieres. 1986. Effect of insulin on glucose uptake and metabolism in human placenta. *J. Clin. Endocrinol. & Metab.*, 62:803-807.

Chen, E. Y., Y.-C. Liao, D. H. Smith, H. A. Barrera-Saldaño, R. E. Gelinas, and P. H. Seeburg. 1989. The human growth hormone locus: nucleotide sequence, biology, and evolution. *Genomics*, 4:479-497.

Chevalier-Clément, F. 1989. Pregnancy loss in the mare. *Anim. Reprod. Sci.*, 20:231-244.

Chua, S., T. Wilkins, I. Sargent, and C. Redman. 1991. Trophoblast deportation in pre-eclamptic pregnancy. *Br. J. Obstet. Gynaecol.*, 98:973-979.

Clayton-Smith, J. 1992. Angelman's syndrome. *Arch. Dis. Child.*, 67:889-891.

Cole, L. A., A. Kardana, S.-Y. Park, and G. D. Braunstein. 1993. The deactivation of hCG by nicking and dissociation. *J. Clin. Endocrinol. & Metab.*, 76:704-710.

Cooper, D. W., S. P. Brennecke, and A. N. Wilton. 1993. Genetics of pre-eclampsia. *Hypertens. Preg.*, 12:1-23.

Counts, D. R., H. Gwirtsman, L. M. S. Carlsson, M. Lesem, and G. B. Cutler. 1992. The effect of anorexia nervosa and refeeding on growth hormone-binding protein, the insulin-like growth factors (IGFs), and the IGF-binding proteins. *J. Clin. Endocrinol. & Metab.*, 75:762-767.

Csapo, A. I., M. O. Pulkkinen, B. Ruttner, J. P. Sauvage, and W. G. Wiest. 1972. The significance of the human corpus luteum in pregnancy maintenance. I. Preliminary studies. *Am. J. Obstet. Gynecol.*, 112:1061-1067.

Csapo, A. I., M. O. Pulkkinen, and W. G. Wiest. 1973. Effects of luteectomy and progesterone replacement therapy in early pregnant patients. *Am. J. Obstet. Gynecol.*, 115:759-765.

Cunningham, B. C., and J. A. Wells. 1991. Rational design of receptor-specific variants of human growth hormone. *Proc. Natl. Acad. Sci. USA*, 88:3407-3411.

Cusson, J. R., J. Gutskowska, E. Rey, N. Michon, M. Boucher, and P. Larochelle. 1985. Plasma concentrations of atrial natriuretic factor in normal pregnancy. *N. Engl. J. Med.*, 313: 1230-1231.

Damm, P., C. Kühl, A. Bertelsen, and L. Mølsted-Pedersen. 1992. Predictive factors for the development of diabetes in women with previous gestational diabetes mellitus. *Am. J. Obstet. Gynecol.*, 167:607-616.

Daughaday, W. H. 1989. Growth hormone: normal synthesis, secretion, control, and mechanisms of action. In L. J. DeGroot (ed.), *Endocrinology*, 2nd ed., pp. 318-329. W. B. Saunders, Philadelphia.

Daughaday, W. H., and D. M. Kipnis. 1966. The growth-promoting and anti-insulin actions of somatotropin. *Recent Progr. Horm. Res.*, 22:49-99.

Davidson, M. B. 1987. Effect of growth hormone on carbohydrate and lipid metabolism. *Endocr. Rev.*, 8:115-131.

Deanesly, R. 1966. The endocrinology of pregnancy and foetal life. In A. S. Parkes (ed.), *Marshall's Physiology of Reproduction*, Vol. III, 3rd ed., pp. 891-1063. Longman's, Green and Company, London.

de Boer, K., J. W. ten Cate, A. Sturk, J. J. J. Borm, and P. E. Treffers. 1989. Enhanced thrombin generation in normal and hypertensive pregnancies. *Am. J. Obstet. Gynecol.*, 160: 95-100.

DeChiara, T. M., A. Efstratiadis, and E. J. Robertson. 1990. A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. *Nature*, 345:78-80.

DeChiara, T. M., E. J. Robertson, and A. Efstratiadis. 1991. Parental imprinting of the mouse insulin-like growth factor II gene. *Cell*, 64:849-859.

De Feo, P., G. Perriello, E. Torlone, M. M. Ventura, C. Fanelli, P. Brunetti, J. E. Gerich, and G. B. Bolli. 1989. Demonstration of a role for growth hormone in glucose counterregulation. *Am. J. Physiol.*, 256:E835-E843.

Dencker, S. J., G. Johansson, and I. Milsom. 1992. Quantification of naturally occurring benzodiazepine-like substances in human breast milk. *Psychopharmacology*, 107:69-72.

Dennefors, B., A. Sjögren, and L. Hamberger. 1982. Progesterone and adenosine 3′, 5′-monophosphate formation by isolated corpora lutea of different ages: influence of human chorionic gonadotropin and prostaglandins. *J. Clin. Endocrinol. & Metab.*, 55:102-107.

Depue, R. H., L. Bernstein, R. K. Ross, H. L. Judd, and B. E. Henderson. 1987. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. *Am. J. Obstet. Gynecol.*, 156:1137-1141.

Dietl, J., P. Ruck, K. Marzusch, H.-P. Horny, E. Kaiserling, and R. Handgretinger. 1992. Uterine granular lymphocytes are activated natural killer cells expressing VLA-1. *Immunol. Today*, 13:236.

Dietz, A. B., M. Georges, D. W. Threadgill, J. E. Womack, and L. A. Schuler. 1992. Somatic cell mapping, polymorphism, and linkage analysis of bovine prolactin-related proteins and placental lactogen. *Genomics*, 14:137-143.

Dokras, A., I. L. Sargent, C. Ross, R. L. Gardner, and D. H. Barlow. 1991. The human blastocyst: morphology and human chorionic gonadotropin secretion in vitro. *Hum. Reprod.* (*Oxf.*), 6:1143-1151.

Dornhorst, A., P. C. Bailey, V. Anyaoku, R. S. Elkeles, D. G. Johnston, and R. W. Beard. 1990. Abnormalities of glucose tolerance following gestational diabetes. *Q. J. Med.*, 77: 1219-1228.

Dougherty, C. M., C. Cunningham, and A. Mickal. 1978. Choriocarcinoma with metastasis in a postmenopausal woman. *Am. J. Obstet. Gynecol.*, 132:700-701.

Douglas, G. W., L. Thomas, M. Carr, N. M. Cullen, and R. Morris. 1959. Trophoblast in the circulating blood during pregnancy. *Am. J. Obstet. Gynecol.*, 78:960-973.

Duquesnoy, P., M. L. Sobrier, S. Amselem, and M. Goossens. 1991. Defective membrane expression of human growth hormone (GH) receptor causes Laron-type GH insensitivity syndrome. *Proc. Natl. Acad. Sci. USA*, 88:10272-10276.

Easterling, T. R., T. J. Benedetti, B. C. Schmucker, and S. P. Millard. 1990. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet. Gynecol.*, 76:1061-1069.

Edmonds, D. K., K. S. Lindsay, J. F. Miller, E. Williamson, and P. J. Wood. 1982. Early embryonic mortality in women. *Fertil. Steril.*, 38:447-453.

Eiben, B., S. Borgmann, I. Schübbe, and I. Hansmann. 1987. A cytogenetic study directly from chorionic villi of 140 spontaneous abortions. *Hum. Genet.*, 77:137-141.

Elders, M. J., J. T. Garland, W. H. Daughaday, D. A. Fisher, J. E. Whitney, and E. R. Hughes. 1973. Laron's dwarfism: studies on the nature of the defect. *J. Pediatr.*, 83:253-263.

Ellis, S. A., M. S. Palmer, and A. J. McMichael. 1990. Human trophoblast and the choriocarcinoma line BeWo express a truncated HLA class I molecule. *J. Immunol.*, 144:731-735.

Eriksson, L., F. Frankenne, S. Edèn, G. Hennen, and B. von Schoultz. 1989. Growth hormone 24-h serum profiles during pregnancy—lack of pulsatility for the secretion of the placental variant. *Br. J. Obstet. Gynaecol.*, 96:949-953.

Evans, A. J., T. C. Li, C. Selby, and W. J. Jeffcoate. 1986. Morning sickness and thyroid function. *Br. J. Obstet. Gynaecol.*, 93:520-522.

Fairweather, D. V. I. 1968. Nausea and vomiting in pregnancy. *Am. J. Obstet. Gynecol.*, 102:135-175.

Farmer, G., D. R. Hamilton-Nicol, H. W. Sutherland, I. S. Ross, G. Russell, and D. W. M. Pearson. 1992. The range of insulin response and glucose tolerance in lean, normal, and obese women during pregnancy. *Am. J. Obstet. Gynecol.*, 167:772-777.

Farrer-Brown, G., J. O. W. Beilby, and M. H. Tarbit. 1970a. The blood supply of the uterus. 1. Arterial vasculature. *J. Obstet. Gynaecol. Br. Commonw.*, 77:673-681.

———, ———, and ———. 1970b. The blood supply of the uterus. 1. Venous pattern. *J. Obstet. Gynaecol. Br. Commonw.*, 77:682-689.

Fay, T. N., and J. G. Grudzinskas. 1991. Human endometrial peptides a review of their potential role in implantation and placentation. *Hum. Reprod.* (*Oxf.*), 6:1311-1326.

Ferenczy, A. 1987. Anatomy and histology of the uterine corpus. In R. J. Kurman (ed.), *Blaustein's Pathology of the Female Genital Tract*, 3rd ed., pp. 257-291. Springer-Verlag, New York.

Ferry, B. L., I. L. Sargent, P. M. Starkey, and C. W. G. Redman. 1991. Cytotoxic activity against trophoblast and choriocarcinoma cells of large granular lymphocytes from human early pregnancy decidua. *Cell. Immunol.*, 132: 140-149.

Ferry, B. L., P. M. Starkey, I. L. Sargent, G. M. O. Watt, M. Jackson, and C. W. G. Redman. 1991. Cell populations in the human early pregnancy decidua: natural killer activity and response to interleukin-2 of CD56-positive large granular lymphocytes. *Immunology*, 70: 446-452.

Finberg, R. W., W. White, and A. Nicholson-Weller. 1992. Decay accelerating factor expression on either effector or target cells inhibits cytotoxicity by human natural killer cells. *J. Immunol.*, 149:2055-2060.

Fletcher, A. P., N. K. Alkjaersig, and R. Burstein. 1979. The influence of pregnancy upon blood coagulation and plasma fibrinolytic enzyme function. *Am. J. Obstet. Gynecol.*, 134:743-751.

Folkow, B., and E. Neil. 1971. *Circulation.* Oxford University Press, New York.

Forejt, J., and S. Gregorová. 1992. Genetic analysis of genomic imprinting: an *imprintor-1* gene controls inactivation of the paternal copy of the mouse *Tme* locus. *Cell*, 70:443-450.

Fothergill, W. E. 1899. The function of the decidual cell. *Edinb. Med. J.*, 5:265-273.

Frankenne, F., J. Closset, F. Gomez, M. L. Scippo, J. Smal, and G. Hennen. 1988. The physiology of growth hormones (GHs) in pregnant women and partial characterization of the placental GH variant. *J. Clin. Endocrinol. & Metab.*, 66:1171-1180.

Frassi, L. 1907. Über ein junges menschliches Ei in situ. *Arch. mikroscop. Anat. Entwicklungsgeschichte*, 70:492-505.

———. 1908. Weitere Ergebnisse des Studiums eines jungen menschlichen Ei in situ. *Arch. mikroscop. Anat. Entwicklungsgeschichte*, 71:667–694.

Friedman, S. A., R. N. Taylor, and J. M. Roberts. 1991. Pathophysiology of preeclampsia. *Clin. Perinatol.*, 18:661–682.

Gerretsen, G., H. J. Huisjes, M. J. Hardonk, and J. D. Elema. 1983. Trophoblast alterations in the placental bed in relation to physiological changes in spiral arteries. *Br. J. Obstet. Gynaecol.*, 90:34–39.

Giannoukakis, N., C. Deal, J. Paquette, C. G. Goodyer, and C. Polychronakos. 1993. Parental genomic imprinting of the human IGF2 gene. *Nature Genet.*, 4:98–101.

Ginsburg, J., and S. L. B. Duncan. 1967. Peripheral blood flow in normal pregnancy. *Cardiovasc. Res.*, 1:132–137.

Girard, J., and P. Ferre. 1982. Metabolic and hormonal changes around birth. In C. T. Jones (ed.), *The Biochemical Development of the Fetus and Neonate*, pp. 517–551. Elsevier, Amsterdam.

Giudice, L. C., B. A. Dsupin, and J. C. Irwin. 1992. Steroid and peptide regulation of insulin-like growth factor binding proteins secreted by human endometrial stromal cells is dependent on stromal differentiation. *J. Clin. Endocrinol. & Metab.*, 75:1235–1241.

Godfrey, K. M., C. W. G. Redman, D. J. P. Barker, and C. Osmond. 1991. The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight. *Br. J. Obstet. Gynaecol.*, 98:886–891.

Godowski, P. J., D. W. Leung, L. R. Meacham, J. P. Galgani, R. Hellmiss, R. Keret, P. S. Rotwein, J. S. Parks, Z. Laron, and W. I. Wood. 1989. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. *Proc. Natl. Acad. Sci. USA*, 86:8083–8087.

Goodwin, T. M., M. Montoro, and J. H. Mestman. 1992. Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. *Am. J. Obstet. Gynecol.*, 167:648–652.

Goodwin, T. M., M. Montoro, J. H. Mestman, A. E. Pekary, and J. M. Hershman. 1992. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. *J. Clin. Endocrinol. & Metab.*, 75:1333–1337.

Gräfenberg, E. 1910. Beiträge zur Physiologie der Eieinbettung. *Z. Geburtshülfe Gynäkol.*, 65:1–35.

Graham, C. H., and P. K. Lala. 1991. Mechanism of control of trophoblast invasion in situ. *J. Cell. Physiol.*, 148:228–234.

Graham, C. H., J. J. Lysiak, K. R. McRae, and P. K. Lala. 1992. Localization of transforming growth factor-β at the human fetal-maternal interface: role in trophoblast growth and differentiation. *Biol. Reprod.*, 46:561–572.

Grosser, O. 1933. Human and comparative placentation, including the early stages of human development. *Lancet*, 1:999–1001, 1053–1058.

Grumbach, M. M., S. L. Kaplan, C. L. Abrams, J. J. Bell, and F. A. Conle. 1966. Plasma free fatty acid response to the administration of chorionic "growth-hormone-prolactin." *J. Clin. Endocrinol. & Metab.*, 26:478–482.

Grumbach, M. M., S. L. Kaplan, J. J. Sciarra, and I. M. Burr. 1968. Chorionic growth hormone-prolactin (CPG): secretion, disposition, biologic activity in man, and postulated function as the "growth hormone" of the second half of pregnancy. *Ann. N. Y. Acad. Sci.*, 148:501–531.

Grünberger, W., S. Leodolter, and O. Parschalk. 1979. Maternal hypotension: fetal outcome in treated and untreated cases. *Gynecol. Obstet. Invest.*, 10:32–38.

Guillou, F., and Y. Combarnous. 1983. Purification of equine gonadotropins and comparative structure of their acid-dissociation and receptor-binding specificity. *Biochim. Biophys. Acta*, 755:229–236.

Gustafson, A. B., M. F. Banasiak, R. K. Kalkhoff, T. C. Hagen, and H.-J. Kim. 1980. Correlation of hyperprolactinemia with altered plasma insulin and glucagon: similarity to effects of late human pregnancy. *J. Clin. Endocrinol. & Metab.*, 51:242–246.

Hahlin, M., B. Lindblom, A. Schuurs, H. Kloosterboer, and L. Hamberger. 1989. Characterization of a monoclonal antibody which inhibits the biological activity of human chorionic gonadotropin in human corpora lutea. *Hum. Reprod. (Oxf.)*, 4:152–157.

Haig, D. 1990. Brood reduction and optimal parental investment when offspring differ in quality. *Am. Nat.*, 136:550–556.

———. 1992. Genomic imprinting and the theory of parent-offspring conflict. *Semin. Devel. Biol.*, 3:153–160.

Haig, D., and A. Grafen. 1991. Genetic scrambling as a defence against meiotic drive. *J. Theor. Biol.*, 153:531–558.

Haig, D., and C. Graham. 1991. Genomic imprinting and the strange case of the insulin-like growth factor-II receptor. *Cell*, 64:1045–1046.

Haig, D., and M. Westoby. 1989. Parent-specific gene expression and the triploid endosperm. *Am. Nat.*, 134:147–155.

Hall, K., U. Hansson, G. Lundin, M. Luthman, B. Persson, G. Póvoa, M. Stangenberg, and U. Öfverholm. 1986. Serum levels of somatomedins and somatomedin-binding protein in pregnant women with type I or gestational diabetes and their infants. *J. Clin. Endocrinol. & Metab.*, 63:1300-1306.

Hanson, F. W., J. E. Powell, and V. C. Stevens. 1971. Effects of HCG and human pituitary LH on steroid secretion and functional life of the human corpus luteum. *J. Clin. Endocrinol. & Metab.*, 32:211-215.

Harris, J. W. S., and E. M. Ramsey. 1966. The morphology of human uteroplacental vasculature. *Carnegie Inst. Washington Publ.* 625, *Contrib. Embryol.*, 38:43-58.

Harrison, K. B. 1989. X-chromosome inactivation in the human cytotrophoblast. *Cytogenet. Cell Genet.*, 52:37-41.

Hauguel, S., J. C. Challier, and V. Desmaizieres. 1986. Glucose uptake, utilization, and transfer by the human placenta as functions of maternal glucose concentration. *Pediatr. Res.*, 20:269-273.

Hershman, J. M. 1992. Editorial: role of human chorionic gonadotropin as a thyroid stimulator. *J. Clin. Endocrinol. & Metab.*, 74:258-259.

Hoff, J. D., M. E. Quigley, and S. S. C. Yen. 1983. Hormonal dynamics at midcycle: a reevaluation. *J. Clin. Endocrinol. & Metab.*, 57: 792-796.

Hogden, G. D., and J. Itskovitz. 1988. Recognition and maintenance of pregnancy. In E. Knobill and J. D. Neill (eds.), *The Physiology of Reproduction*, pp. 1995-2021. Raven Press, New York.

Holers, V., T. Kinoshita, and H. Molina. 1992. The evolution of mouse and human complement C3-binding proteins: divergence of form but conservation of function. *Immunol. Today*, 13:231-236.

Holmes, C. H., K. L. Simpson, S. D. Wainwright, C. G. Tate, J. M. Houlihan, I. H. Sawyer, I. P. Rogers, F. A. Spring, D. J. Anstee, and M. J. Tanner. 1990. Preferential expression of the complement regulatory protein decay accelerating factor at the fetomaternal interface during human pregnancy. *J. Immunol.*, 144:3099-3105.

Howell, R. J. S., L. A. Perry, N. S. Choglay, H. Bohn, and T. Chard. 1985. Placental protein 12 (PP12): a new test for the prediction of the small-for-gestational-age infant. *Br. J. Obstet. Gynaecol.*, 92:1141-1144.

Hsi, B.-L., J. S. Hunt, and J. P. Atkinson. 1991. Differential expression of complement regulatory proteins on subpopulations of human trophoblast cells. *J. Reprod. Immunol.*, 19:209-223.

Huhtala, M.-L., M. Seppälä, A. Närvänen, P. Palomäki, M. Julkunen, and H. Bohn. 1987. Amino acid sequence homology between human placental protein 14 and β-lactoglobulins from various species. *Endocrinology*, 120: 2620-2622.

Hunt, J. S., and H. T. Orr. 1992. HLA and maternal-fetal recognition. *FASEB (Fed. Am. Soc. Exp. Biol.) J.*, 6:2344-2348.

Hunter, J. 1786. *Observations on Certain Parts of the Animal Oeconomy*. London.

Hustin, J., and J.-P. Schaaps. 1987. Echocardiographic and anatomic studies of the maternotrophoblastic border during the first trimester of pregnancy. *Am. J. Obstet. Gynecol.*, 157:162-168.

Jackson-Grusby, L. L., D. Pravtcheva, F. H. Ruddle, and D. I. H. Linzer. 1988. Chromosomal mapping of the prolactin/growth hormone gene family in the mouse. *Endocrinology*, 122:2462-2466.

Järnfelt-Samsioe, A. 1987. Nausea and vomiting in pregnancy: a review. *Obstet. Gynecol. Surv.*, 42:422-427.

Järnfelt-Samsioe, A., G. Samsioe, and G.-M. Velinder. 1983. Nausea and vomiting in pregnancy—a contribution to its epidemiology. *Gynecol. Obstet. Invest.*, 16:221-229.

Järnfelt-Samsioe, A., B. Eriksson, K.-H. Leissner, and G. Samsioe. 1985. Gallbladder disease related to use of oral contraceptives and nausea in pregnancy. *South. Med. J.*, 78:1040-1043.

Jeffcoate, T. N. A. 1966. Pre-eclampsia and eclampsia: the disease of theories. *Proc. R. Soc. Med.*, 59:397-404.

Jeffcoate, W. J., and C. Bain. 1985. Recurrent pregnancy-induced thyrotoxicosis presenting as hyperemesis gravidarum. Case report. *Br. J. Obstet. Gynaecol.*, 92:413-415.

Jia, X.-C., M. Oikawa, M. Bo, T. Tanaka, T. Ny, I. Boime, and A. J. W. Hsueh. 1991. Expression of human luteinizing hormone (LH) receptor: interaction with LH and chorionic gonadotropin from human but not equine, rat, and ovine species. *Mol. Endocrinol.*, 5:759-768.

Johnson, L. W., and C. H. Smith. 1980. Monosaccharide transport across microvillous membrane of human placenta. *Am. J. Physiol.*, 238: C160-C168.

———, and ———. 1985. Glucose transport across the basal plasma membrane of human placental syncytiotrophoblast. *Biochim. Biophys. Acta*, 815:44-50.

Johnstone, R. W. 1914. Contribution to the study of the early human ovum based upon the investigation of I. A very early ovum embedded in the uterus and II. A very early ovum embedded in the infundibulum of the tube. *J. Obstet. Gynaecol. Br. Emp.*, 25:231-276.

Josimovich, J. B., K. Merisko, and L. Boccella. 1977. Amniotic prolactin control over amniotic and fetal extracellular fluid water and electrolytes in the rhesus monkey. *Endocrinology*, 100: 564-570.

Kajii, T., and K. Ohama. 1977. Androgenetic origin of hyatidiform mole. *Nature*, 268:633-634.

Kardana, A., M. M. Elliott, M. Gawinowicz, S. Birken, and L. A. Cole. 1991. The heterogeneity of human chorionic gonadotropin (hCG). I. Characterization of peptide heterogeneity in 13 individual preparations. *Endocrinology*, 129: 1541-1550.

Karn, M. N., and L. S. Penrose. 1951. Birth weight and gestation time in relation to maternal age, parity and infant survival. *Ann. Eugenics*, 16:147-164.

Katz, R., J. S. Karliner, and R. Resnik. 1978. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation*, 58:434-441.

Kauma, S., and S. S. Shapiro. 1986. Immunoperoxidase localization of prolactin in endometrium during normal menstrual, luteal phase defect, and corrected luteal phase defect cycles. *Fertil. Steril.*, 46:37-41.

Kelly, P. A., J. Djiane, M.-C. Postel-Vinay, and M. Edery. 1991. The prolactin/growth hormone receptor family. *Endocr. Rev.*, 12:235-251.

Khan, W. N., S. Teglund, K. Bremer, and S. Hammarström. 1992. The pregnancy-specific glycoprotein family of the immunoglobulin superfamily: identification of new members and estimation of family size. *Genomics*, 12:780-787.

Khong, T. Y., F. de Wolf, W. B. Robertson, and I. Brosens. 1986. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational-age infants. *Br. J. Obstet. Gynaecol.*, 93:1049-1059.

Kim, Y. J., and P. Felig. 1971. Plasma chorionic somatomammotropin levels during starvation in mid-pregnancy. *J. Clin. Endocrinol. & Metab.*, 32:864-867.

King, A., N. Balendran, P. Wooding, N. P. Carter, and Y. W. Loke. 1991. CD3-leukocytes present in the human uterus during early placentation: phenotypic and morphologic characterization of the $CD56^{++}$ population. *Dev. Immunol.*, 1:169-190.

King, A., and Y. W. Loke. 1990. Trophoblast and JEG choriocarcinoma cells are sensitive to lysis by IL-2 stimulated decidual LGL. *Cell. Immunol.*, 132:140-149.

———, and ———. 1991. On the nature and function of human uterine granular lymphocytes. *Immunol. Today*, 12:432-435.

Kisalus, L. L., and J. C. Herr. 1988. Immunocytochemical localization of heparan sulfate proteoglycan in human decidual cell secretory bodies and placental fibrinoid. *Biol. Reprod.*, 39: 419-430.

Kisalus, L. L., J. C. Herr, and C. D. Little. 1987. Immunolocalization of extracellular matrix proteins and collagen synthesis in first-trimester human decidua. *Anat. Rec.*, 218:402-415.

Kleine, H. O. 1931. Zur Systematik der Pathologie der sogenannte Durchdringungszone. Unter besonderer Berücksichtigung der Genese von Blasenmole und Chorionepitheliom. *Arch. Gynaekol.*, 145:459-473.

Kletzky, O. A., F. Rossman, S. I. Bertolli, L. D. Platt, and D. R. Mishell. 1985. Dynamics of human chorionic gonadotropin, prolactin, and growth hormone in serum and amniotic fluid throughout normal human pregnancy. *Am. J. Obstet. Gynecol.*, 151:878-884.

Klopper, A. 1980. The new placental proteins. *Placenta*, 1:77-89.

Kühl, C. 1991. Insulin secretion and insulin resistance in pregnancy and GDM. *Diabetes*, 40 (Suppl. 2):18-24.

Kühl, C., P. Goede, J. G. Klebe, and J. Pedersen. 1975. Human placental lactogen concentration during physiological fluctuations of serum glucose in normal pregnant and gestational diabetic women. *Acta Endocrocinol.*, 80:365-373.

Kuijpers, T. W., M. Hoogerwerf, L. J. van der Laan, G. Nagel, C. E. van der Schoot, F. Grunert, and D. Roos. 1992. CD66 nonspecific cross-reacting antigens are involved in neutrophil adherence to cytokine-activated endothelial cells. *J. Cell Biol.*, 118:457-466.

Kurman, R. J. 1991. Pathology of trophoblast. In F. T. Kraus, I. Damjanov, and N. Kaufman (eds.), *Pathology of Reproductive Failure*, pp. 195-227. Williams & Wilkins, Baltimore.

Kuroki, M., F. Arakawa, Y. Matsuo, S. Oikawa, Y. Misumi, H. Nakazato, and Y. Matsuoka. 1991. Molecular cloning of nonspecific cross-reacting antigens in human granulocytes. *J. Biol. Chem.*, 266:11810-11817.

Labarrere, C. A., and W. P. Faulk. 1991. Anchoring villi in human placental basal plate: lymphocytes, macrophages and coagulation. *Placenta*, 12:173-182.

Lai, W. H., H. J. Guyda, C. L. Branchaud, and C. G. Goodyer. 1985. Insulin-induced receptor regulation in early gestation and term human placental cell cultures. *Placenta*, 6:505-517.

Landgraf, R., M. M. C. Landgraf-Leurs, A. Weissmann, R. Hörl, K. von Werder, and P. C. Scriba. 1977. Prolactin: a diabetogenic hormone. *Diabetologia*, 13:99-104.

Lathrop, J. C., T. J. Wachtel, and G. F. Meissner. 1978. Uterine choriocarcinoma fourteen years following bilateral tubal ligation. *Obstet. Gynecol.*, 51:477-482.

Lee, H., C. D. Gregory, G. B. Rees, I. V. Scott, and P. R. Golding. 1987. Cytotoxic activity and phenotypic analysis of natural killer cells in early normal human pregnancy. *J. Reprod. Immunol.*, 12:35-47.

Lees, M. M., S. H. Taylor, D. B. Scott, and M. G. Kerr. 1967. A study of cardiac output at rest throughout pregnancy. *J. Obstet. Gynaecol. Br. Commonw.*, 74:319-328.

Leff, S. E., C. I. Brannan, M. L. Reed, T. Özçelik, U. Francke, N. G. Copeland, and N. A. Jenkins. 1992. Maternal imprinting of the mouse *Snrpn* gene and conserved linkage homology with the human Prader-Willi syndrome region. *Nature Genet.*, 2:259-264.

Librach, C. L., Z. Werb, M. L. Fitzgerald, K. Chiu, N. M. Corwin, R. A. Esteves, D. Grobelny, R. Galardy, C. H. Damsky, and S. J. Fisher. 1991. 92-kD type IV collagenase mediates invasion of human cytotrophoblasts. *J. Cell Biol.*, 113:437-449.

Liedholm, P., and B. Åstedt. 1976. Inhibitory effect of decidua on fibrinolysis induced by urokinase and by the fibrinolytic activity of the rat ovum. *Acta Obstet. Gynecol. Scand.*, 55:217-219.

Lind, T., and M. Aspillaga. 1988. Metabolic changes during normal and diabetic pregnancy. In E. A. Reece and D. R. Coustan (eds.), *Diabetes Mellitus in Pregnancy: Principles and Practice*, pp. 75-102. Churchill Livingstone, New York.

Lind, T., S. Bell, E. Gilmore, H. J. Huisjes, and A. V. Schally. 1977. Insulin disappearance rate in pregnant and non-pregnant women, and in non-pregnant women given GHRIH. *Eur. J. Clin. Invest.*, 7:47-51.

Lindor, N. M., J. A. Ney, T. A. Gaffey, R. B. Jenkins, S. N. Thibodeau, and G. W. Dewald. 1992. A genetic review of complete and partial hydatidiform moles and nonmolar triploidy. *Mayo Clin. Proc.*, 67:791-799.

Ljunggren, H.-G., and K. Kärre. 1990. In search of the 'missing self': MHC molecules and NK cell recognition. *Immunol. Today*, 11:237-244.

Loke, Y. W., A. King, and A. Grabowska. 1990. Antigenic expression by migrating trophoblast and its relevance to implantation. In H.-W. Denker and J. D. Aplin (eds.), *Trophoblast Invasion and Endometrial Receptivity*, pp. 191-207. Plenum Press, New York.

Lowman, H. B., B. C. Cunningham, and J. A. Wells. 1991. Mutational analysis and protein engineering of receptor-binding determinants in human placental lactogen. *J. Biol. Chem.*, 266:10982-10988.

Luckett, W. P. 1974. Comparative development and evolution of the placenta in primates. *Contrib. Primatol.*, 3:142-234.

MacDonald, P. C., R. A. Dombroski, and M. L. Casey. 1991. Recurrent secretion of progesterone in large amounts: an endocrine/metabolic disorder unique to young women? *Endocr. Rev.*, 12:372-401.

MacGillivray, I. 1958. Some observations on the incidence of pre-eclampsia. *J. Obstet. Gynaecol. Br. Emp.*, 65:536-539.

MacGillivray, I., G. A. Rose, and B. Rowe. 1969. Blood pressure survey in pregnancy. *Clin. Sci. (Lond.)*, 37:395-407.

MacLeod, J. N., I. Worsley, J. Ray, H. G. Friesen, S. A. Liebhaber, and N. E. Cooke. 1991. Human growth hormone-variant is a biologically active somatogen and lactogen. *Endocrinology*, 128:1298-1302.

Magenis, R. E., S. Toth-Fejel, L. J. Allen, M. Black, M. G. Brown, S. Budden, R. Cohen, J. M. Friedman, D. Kalousek, J. Zonana, D. Lacy, S. LaFranchi, M. Lahr, J. MacFarlane, and C. P. S. Williams. 1990. Comparison of the 15q deletions in Prader-Willi and Angelman syndromes: specific regions, extent of deletions, parental origin, and clinical consequences. *Am. J. Med. Genet.*, 35:333-349.

Maslar, I. A., B. M. Kaplan, A. A. Luciano, and D. H. Riddick. 1979. Prolactin production by the endometrium of early human pregnancy. *J. Clin. Endocrinol. & Metab.*, 51:78-83.

Masson, G. M., F. Anthony, and E. Chau. 1985. Serum chorionic gonadotrophin (hCG), schwangerschaftsprotein 1 (SP1), progesterone and oestradiol levels in patients with nausea and vomiting in early pregnancy. *Br. J. Obstet. Gynaecol.*, 92:211-215.

McCausland, A. M., C. Hyman, T. Winsor, and A. D. Trotter. 1961. Venous distensibility during pregnancy. *Am. J. Obstet. Gynecol.*, 81:472-479.

McFadden, D. E., and D. K. Kalousek. 1991. Two different phenotypes of fetuses with chromosomal triploidy: correlation with parental origin of the extra haploid set. *Am. J. Med. Genet.*, 38:535-538.

McKay, D. G. 1981. Chronic intravascular coagulation in normal pregnancy and preeclampsia. *Contrib. Nephrol.*, 25:108-119.

McKeown, T., and R. G. Record. 1953. Observations on foetal growth in multiple pregnancies in man. *J. Endocrinol.*, 8:386-401.

McParland, P., and J. M. Pearce. 1988. Doppler blood flow in pregnancy. *Placenta*, 9:427-450.

Medawar, P. B. 1953. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates, *Symp. Soc. Exp. Biol.*, 7:320-337.

Milsom, I., J. Hedner, and T. Hedner. 1988. Plasma atrial natriuretic peptide (ANP) and maternal hemodynamic changes during normal pregnancy. *Acta Obstet. Gynecol. Scand.*, 67: 717-722.

Moll, U. M., and B. L. Lane. 1990. Proteolytic activity of first trimester human placenta: localization of interstitial collagenase in villous and extravillous trophoblast. *Histochemistry*, 94: 555-560.

Moll, W., and W. Künzel. 1973. The blood pressure in arteries entering the placentae of guinea pigs, rats, rabbits, and sheep. *Pfluegers Arch. Eur. J. Physiol.*, 338:125-131.

Moll, W., W. Künzel, and J. Herberger. 1974. Hemodynamic implications of hemochorial placentation. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 5:67-74.

Moll, W., W. Künzel, L. A. M. Stolte, J. Kleinhout, P. A. de Jong, and A. F. L. Veth. 1974. The blood pressure in the decidual part of the uteroplacental arteries (spiral arteries) of the rhesus monkey. *Pfluegers Arch. Eur. J. Physiol.*, 346:291-297.

Moore, T., and D. Haig. 1991. Genomic imprinting in mammalian development: a parental tug-of-war. *Trends Genet.*, 7:45-49.

Moran, P., H. Beasley, A. Gorrell, E. Martin, P. Gribling, H. Fuchs, N. Gillett, L. E. Burton, and I. W. Caras. 1992. Human recombinant decay accelerating factor inhibits complement activation in vitro and in vivo. *J. Immunol.*, 149: 1736-1743.

Mori, M., N. Amino, H. Tamaki, K. Miyai, and O. Tanizawa. 1988. Morning sickness and thyroid function in normal pregnancy. *Obstet. Gynecol.*, 72:355-359.

Mossman, H. W. 1937. Comparative morphogenesis of the fetal membranes and accessory uterine structures. *Carnegie Inst. Washington Publ.* 479, *Contrib. Embryol.*, 26:129-246.

———. 1987. *Vertebrate Fetal Membranes*. Rutgers University Press, New Brunswick.

———. 1991. Classics revisited: comparative morphogenesis of the fetal membranes and accessory uterine structures. *Placenta*, 12:1-5.

Moutou, C., C. Junien, I. Henry, and C. Bonaïti-Pellié. 1992. Beckwith-Wiedemann syndrome: a demonstration of the mechanisms responsible for the excess of transmitting females. *J. Med. Genet.*, 29:217-220.

Murphy, B. D., and S. D. Martinuk. 1991. Equine chorionic gonadotropin. *Endocr. Rev.*, 12:27-44.

Naeye, R. L. 1981a. Nutritional/nonnutritional interactions that affect the outcome of pregnancy. *Am. J. Clin. Nutr.*, 34:727-731.

———. 1981b. Maternal blood pressure and fetal growth. *Am. J. Obstet. Gynecol.*, 141:780-787.

Naeye, R. L., and E. A. Friedman. 1979. Causes of perinatal death associated with gestational hypertension and proteinuria. *Am. J. Obstet. Gynecol.*, 133:8-10.

Nelson, D. M., R. M. Smith, and L. Jarett. 1978. Nonuniform distribution and grouping of insulin receptors on the surface of human placental syncytial trophoblast. *Diabetes*, 27:530-538.

Ng, P. H., and W. A. W. Walters. 1992. The effects of chronic maternal hypotension during pregnancy. *Aust. & NZ J. Obstet. & Gynaecol.*, 32:14-16.

Nicholls, R. D., E. M. Rinchik, and D. J. Driscoll. 1992. Genomic imprinting in mammalian development: Prader-Willi and Angelman syndromes as disease models. *Semin. Devel. Biol.*, 3:139-152.

Noyes, R. W., A. T. Hertig, and J. Rock. 1950. Dating the endometrial biopsy. *Fertil. Steril.*, 1: 3-25.

Nwokoro, N., H.-C. Chen, and A. Chrambach. 1981. Physical, biological, and immunological characterization of highly purified urinary human chorionic gonadotropin components separated by gel electrofocusing. *Endocrinology*, 108: 291-299.

O'Brien, B., and N. Newton. 1989. Psyche versus soma: historical evolution of beliefs about nausea and vomiting during pregnancy. *J. Psychosom. Obstet. Gynaecol.*, 12:91-120.

Ogawa, O., M. R. Eccles, J. Szeto, L. A. McNoe, K. Yun, M. A. Maw, P. J. Smith, and A. E. Reeve. 1993. Relaxation of insulin-like growth factor II gene imprinting implicated in Wilm's tumour. *Nature*, 362:749-751.

Ogren, L., and F. Talamantes. 1988. Prolactins of pregnancy and their cellular source. *Int. Rev. Cytol.*, 112:1-66.

Ohlsson, R., L. Holmgren, A. Glaser, A. Szpecht, and S. Pfeifer-Ohlsson. 1989. Insulin-like growth factor 2 and short range stimulatory loops in control of human placental growth. *EMBO J.*, 8:1993-1999.

Ohlsson, R., A. Nyström, S. Pfeifer-Ohlsson, V. Töhönen, F. Hedborg, P. Schofield, F. Flam, and T. J. Ekström. 1993. IGF2 is parentally imprinted during human embryogenesis and in the Beckwith-Wiedemann syndrome. *Nature Genet.*, 4:94-97.

Oikawa, S., C. Inuzuka, M. Kuroki, F. Arakawa, Y. Matsuoka, G. Kosaki, and H. Nakazato. 1991. A specific heterotypic cell adhesion activity between members of carcinoembryonic antigen family, W272 and NCA, is mediated by N-domains. *J. Biol. Chem.*, 266:7995-8001.

Olsen, R. W., and A. J. Tobin. 1990. Molecular biology of $GABA_A$ receptors. *FASEB (Fed. Am. Soc. Exp. Biol.) J.*, 4:1469-1480.

O'Shaughnessy, R. W., R. O'Toole, S. Tuttle, and F. P. Zuspan. 1992. Uterine catecholamines in normal and hypertensive human pregnancy. *Clin. Exp. Hypertens.*, B2:447-457.

Page, E. W. 1939. The relation between hydatid moles, relative ischemia of the gravid uterus and the placental origin of eclampsia. *Am. J. Obstet. Gynecol.*, 37:291-293.

Page, E. W., and R. Christianson. 1976. Influence of blood pressure changes with and without proteinuria upon outcome of pregnancy. *Am. J. Obstet. Gynecol.*, 126:821-833.

Pankow, Dr. 1906. Graviditäts-, Menstruations- und Ovulations-sklerose der Uterus- und Ovarialgefässe. *Arch. Gynaekol.*, 80:271-282.

Parks, J. S. 1989. Molecular biology of growth hormone. *Acta Paediatr. Scand.* (Suppl.), 349: 127-135.

Pearce, J. M., S. Campbell, T. Cohen-Overbeek, G. Hackett, J. Hernandez, and J. P. Royston. 1988. Reference ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the uteroplacental and fetal circulation. *Br. J. Obstet. Gynaecol.*, 95:248-256.

Pekary, A. E., I. M. D. Jackson, T. M. Goodwin, X.-P. Pang, M. D. Hein, and J. M. Hershman. 1993. Increased *in vitro* thyrotropic activity of partially sialated human chorionic gonadotropin extracted from hydatidiform moles of patients with hyperthyroidism. *J. Clin. Endocrinol. & Metab.*, 76:70-74.

Pekonen, F., A.-M. Suikkari, T. Mäkinen, and E.-M. Rutanen. 1988. Different insulin-like growth factor binding species in human placenta and decidua. *J. Clin. Endocrinol. & Metab.*, 67:1250-1257.

Pellegrini, I., J.-J. Lebrun, S. Ali, and P. A. Kelly. 1992. Expression of prolactin and its receptor in human lymphoid cells. *Mol. Endocrinol.*, 6: 1023-1031.

Pierce, J. G., and T. F. Parsons. 1981. Glycoprotein hormones: structure and function. *Annu. Rev. Biochem.*, 50:465-495.

Pijnenborg, R. 1990. Trophoblast invasion and placentation in the human: morphological aspects. In H.-W. Denker and J. D. Aplin (eds.), *Trophoblast Invasion and Endometrial Receptivity*, pp. 33-47. Plenum Press, New York.

Pijnenborg, R., J. Anthony, D. A. Davey, A. Rees, A. Tiltman, L. Vercruysse, and A. van Assche. 1991. Placental bed spiral arteries in the hypertensive disorders of pregnancy. *Br. J. Obstet. Gynaecol.*, 98:648-655.

Pijnenborg, R., J. M. Bland, W. B. Robertson, G. Dixon, and I. Brosens. 1981. The pattern of interstitial trophoblastic invasion of the myometrium in early human pregnancy. *Placenta*, 2:303-316.

Pijnenborg, R., G. Dixon, W. B. Robertson, and I. Brosens. 1980. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. *Placenta*, 1:3-19.

Pijnenborg, R., J. M. Bland, W. B. Robertson, and I. Brosens. 1983. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. *Placenta*, 4: 397-414.

Pijnenborg, R., W. B. Robertson, and I. Brosens. 1985. Morphological aspects of placental ontogeny and phylogeny. *Placenta*, 6:155-162.

Pipe, N. G. J., T. Smith, D. Halliday, C. J. Edmonds, C. Williams, and T. M. Coltart. 1979. Changes in fat, fat-free mass and body water in human normal pregnancy. *Br. J. Obstet. Gynaecol.*, 86:929-940.

Plachot, M. 1989. Chromosome analysis of spontaneous abortions after IVF. A European survey. *Hum. Reprod. (Oxf.)*, 4:425-429.

Policastro, P. F., S. Daniels-McQueen, G. Carle, and I. Boime. 1986. A map of the hCGβ-LHβ gene cluster. *J. Biol. Chem.*, 261:5907-5916.

Profet, M. 1988. The evolution of pregnancy sickness as protection to the embryo against Pleistocene teratogens. *Evol. Theory*, 8:177-190.

———. 1992. Pregnancy sickness as adaptation: a deterrent to maternal ingestion of teratogens. In J. Barkow, L. Cosmides, and J. Tooby (eds.), *The Adapted Mind*, pp. 327-365. Oxford University Press, New York.

———. 1993. Menstruation as a defense against pathogens transported by sperm. *Q. Rev. Biol.*, 68:335-386.

Puistola, U., L. Rönnberg, H. Martikainen, and T. Turpeenniemi-Hujanen. 1989. The human embryo produces basement membrane collagen (type IV collagen)-degrading protease activity. *Hum. Reprod. (Oxf.)*, 4:309-311.

Rachmilewitz, J., O. Gileadi, T. Eldar-Geva, T. Schneider, N. de Groot, and A. Hochberg. 1992. Transcription of the H19 gene in differentiating cytotrophoblasts from human placenta. *Mol. Reprod. Dev.*, 32:196-202.

Rachmilewitz, J., R. Goshen, I. Ariel, T. Schneider, N. de-Groot, and A. Hochberg. 1992. Parental imprinting of the human H19 gene. *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, 309:25-28.

Rage, F., A. Benyassi, S. Arancibia, and L. Tapia-Arancibia. 1992. γ-aminobutyric acid-glutamate interaction in the control of somatostatin release from hypothalamic neurons in primary culture: *in vivo* corroboration. *Endocrinology*, 130: 1056-1062.

Rainier, S., L. A. Johnson, C. J. Dobry, A. J. Ping, P. E. Grundy, and A. P. Feinberg. 1993. Relaxation of imprinted genes in human cancer. *Nature*, 362:747-749.

Ramsey, E. M. 1949. The vascular pattern of the endometrium of the pregnant rhesus monkey (*Macaca mulatta*). *Carnegie Inst. Washington Publ.* 583, *Contrib. Embryol.*, 33:113-148.

Ramsey, E. M., M. L. Houston, and J. W. S. Harris. 1976. Interactions of the trophoblast and maternal tissues in three closely related primate species. *Am. J. Obstet. Gynecol.*, 124:647-652.

Redman, C. W. G. 1989a. Hypertension in pregnancy. In M. de Swiet (ed.), *Medical Disorders in Obstetric Practice*, 2nd ed., pp. 249-305. Blackwell Scientific, Oxford.

———. 1989b. Hypertension in pregnancy. In A. Turnbull and G. Chamberlain (eds.), *Obstetrics*, pp. 515-541. Churchill Livingstone, Edinburgh.

———. 1991. Pre-eclampsia and the placenta. *Placenta*, 12:301-308.

Reiss, R. E., R. W. O'Shaughnessy, T. J. Quilligan, and F. P. Zuspan. 1987. Retrospective comparison of blood pressure course during preeclamptic and matched control pregnancies. *Am. J. Obstet. Gynecol.*, 156:894-898.

Reyes, F. I., R. S. Boroditsky, J. S. D. Winter, and C. Faiman. 1974. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. *J. Clin. Endocrinol. & Metab.*, 38:612-617.

Rivoltini, L., G. Cattoretti, F. Arienti, A. Mastroianni, C. Melani, M. P. Colombo, and G. Parmiani. 1991. The high lysability by LAK cells of colon-carcinoma cells resistant to doxorubicin is associated with high expression of ICAM-1, LFA-3, NCA and a less-differentiated phenotype. *Int. J. Cancer*, 47:746-754.

Rizza, R. A., L. J. Mandarino, and J. E. Gerich. 1982. Effects of growth hormone on insulin action in man. Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. *Diabetes*, 31:663-669.

Roberts, C. J., and C. R. Lowe. 1975. Where have all the conceptions gone? *Lancet*, 1:498-499.

Roberts, J. M., R. N. Taylor, T. J. Musci, D. M. Rodgers, C. A. Hubel, and M. K. McLaughlin. 1989. Preeclampsia: an endothelial cell disorder. *Am. J. Obstet. Gynecol.*, 161:1200-1204.

Robertson, W. B., T. Y. Khong, I. Brosens, F. De Wolf, B. L. Sheppard, and J. Bonnar. 1986. The placental bed biopsy: review from three European centers. *Am. J. Obstet. Gynecol.*, 155:401-412.

Robertson, W. B., and B. Warner. 1974. The ultrastructure of the human placental bed. *J. Pathol.*, 112:203-211.

Rodesch, F., P. Simon, C. Donner, and E. Jauniaux. 1992. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. *Obstet. Gynecol.*, 80:283-285.

Rodgers, G. M., R. N. Taylor, and J. M. Roberts. 1988. Preeclampsia is associated with a serum factor cytotoxic to human endothelial cells. *Am. J. Obstet. Gynecol.*, 159:908-914.

Rosenloecher, K. 1932. Die Veränderungen des Pankreas in der Schwangerschaft bei Mensch und Tier. *Arch. Gynaekol.*, 151:567-575.

Rosenthal, F. D., C. Jones, and S. I. Lewis. 1976. Thyrotoxic vomiting. *Br. Med. J.*, 2:209-211.

Rothchild, I. 1981. The regulation of the mammalian corpus luteum. *Recent Progr. Horm. Res.*, 37:183-298.

Russel, A. S., and C. L. Miller. 1986. Sequential studies on NK cell activity in human pregnancy. *J. Clin. Lab. Immunol.*, 19:5-9.

Ryan, E. A., M. J. O'Sullivan, and J. S. Skyler. 1985. Insulin action during pregnancy. Studies with the euglycemic clamp technique. *Diabetes*, 34:380-389.

Sabharwal, P., R. Glaser, W. Lafuse, S. Varma, Q. Liu, S. Arkins, R. Kooijman, L. Kutz, K. W. Kelley, and W. B. Malarkey. 1992. Prolactin synthesized and secreted by human peripheral blood mononuclear cells: an autocrine growth factor for lymphoproliferation. *Proc. Natl. Acad. Sci. USA*, 89:7713-7716.

Salafia, C. M., J. Xenophon, A. M. Vintzileos, T. Lerer, and L. Silberman. 1990. Fetal growth and placental pathology in maternal hypertensive diseases. *Clin. Exp. Hypertens.*, B9:27-41.

Samaan, N., S. C. C. Yen, D. Gonzalez, and O. H. Pearson. 1968. Metabolic effects of placental lactogen (HPL) in man. *J. Clin. Endocrinol. & Metab.*, 28:485-491.

Schoenek, F. J. 1942. Gonadotropic hormone concentration in emesis gravidarum. *Am. J. Obstet. Gynecol.*, 43:308-312.

Schröder, J., and A. de la Chapelle. 1974. Fetal lymphocytes in the maternal blood. *Blood*, 39: 153-162.

Schröder, J., A. Tiilikainen, and A. de la Chapelle. 1974. Fetal leukocytes in the maternal circulation after delivery. I. Cytological aspects. *Transplantation*, 17:346-354.

Sherman, G. B., M. W. Wolfe, T. A. Farmerie, C. M. Clay, D. S. Threadgill, D. C. Sharp, and J. H. Nilson. 1992. A single gene encodes the β-subunits of equine luteinizing hormone and chorionic gonadotropin. *Mol. Endocrinol.*, 6:951-959.

Sibai, B. M., and W. C. Mabie. 1991. Hemodynamics of preeclampsia. *Clin. Perinatol.*, 18: 727-747.

Simon, P., C. Decoster, H. Brocas, J. Schwers, and G. Vassart. 1986. Absence of human chorionic somatomammotropin during pregnancy associated with two types of gene deletion. *Hum. Genet.*, 74:235-238.

Sinnett, D., J. Wagstaff, K. Glatt, E. Woolf, E. J. Kirkness, and M. Lalande. 1993. High-resolution mapping of the γ-aminobutyric acid receptor subunit β_3 and α_5 gene cluster on chromosome 15q11-q13, and localization of breakpoints in two Angelman syndrome patients. *Am. J. Hum. Genet.*, 52:1216-1229.

Siris, E. S., B. C. Nisula, K. J. Catt, K. Horner, S. Birken, R. E. Canfield, and G. T. Ross. 1978. New evidence for intrinsic follicle-stimulating hormone-like activity in human chorionic gonadotropin and luteinizing hormone. *Endocrinology*, 102:1356-1361.

Socol, M. L., C. P. Weiner, G. Louis, K. Rehnberg, and E. C. Rossi. 1985. Platelet activation in preeclampsia. *Am. J. Obstet. Gynecol.*, 151: 494-497.

Soliman, A. T., A. I. Hassan, M. K. Aref, R. L. Hintz, R. G. Rosenfeld, and A. D. Rogol. 1986. Serum insulin-like growth factor I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein-energy malnutrition before and after nutritional rehabilitation. *Pediatr. Res.*, 20:1122-1130.

Solter, D. 1988. Differential imprinting and expression of maternal and paternal genomes. *Annu. Rev. Genet.*, 22:127-146.

Sorensen, R. L., D. G. Garry, and T. C. Brelje. 1991. Structural and functional considerations of GABA in islets of Langerhans. *Diabetes*, 40: 1365-1374.

Soules, M. R., C. L. Hughes, J. A. Garcia, C. H. Livengood, M. R. Prystowsky, and E. Alexander. 1980. Nausea and vomiting of pregnancy: role of human chorionic gonadotropin and 17-hydroxyprogesterone. *Obstet. Gynecol.*, 55:696-700.

Sowers, J. R., M. B. Zemel, M. F. Walsh, P. R. Standley, P. C. Zemel, R. A. Bronsteen, J. Kraniak, and R. J. Sokol. 1990. Effects of normal pregnancy on cellular cation metabolism and peripheral vascular resistance. *Am. J. Hypertens.*, 3:16-22.

Sparks, J. W. 1984. Human intrauterine growth and nutrient accretion. *Semin. Perinatol. (NY)*, 8:74-93.

Spetz, S. 1964. Peripheral circulation during normal pregnancy. *Acta Obstet. Gynecol. Scand.*, 43: 309-329.

Starkey, P. M. 1992. Natural killer cells/large granular lymphocytes in pregnancy. In C. E. Lewis and J. O'D. McGee (eds.), *The Natural Killer Cell*, pp. 205-240. IRL Press, Oxford.

Starkey, P. M., L. M. Clover, and M. C. P. Rees. 1991. Variation during the menstrual cycle of immune cell populations in human endometrium. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 39: 203-207.

Starkey, P. M., I. L. Sargent, and C. W. G. Redman. 1988. Cell populations in human early pregnancy decidua: characterization and isolation of large granular lymphocytes by flow cytometry. *Immunology*, 65:129-134.

Steel, R. B., J. D. Mosley, and C. H. Smith. 1979. Insulin and placenta: degradation and stabilization, binding to microvillous membrane receptors, and amino acid uptake. *Am. J. Obstet. Gynecol.*, 135:522-529.

Steger, D. J., J. Altschmied, M. Büscher, and P. L. Mellon. 1991. Evolution of placenta-specific gene expression: comparison of the equine and human gonadotropin α-subunit genes. *Mol. Endocrinol.*, 5:243-255.

Stewart, F., and W. R. Allen. 1981. Biological functions and receptor binding activities of equine chorionic gonadotrophins. *J. Reprod. Fertil.*, 62:527-536.

Streydio, C., K. Lacka, S. Swillens, and G. Vassart. 1988. The human pregnancy-specific β_1-glycoprotein (PSβG) and the carcinoembryonic antigen (CEA)-related proteins are members of the same multigene family. *Biochem. Biophys. Res. Commun.*, 154:130-137.

Studd, J. 1973. The origin and effects of proteinuria in pregnancy. *J. Obstet. Gynaecol. Br. Commonw.*, 80:872-883.

Symonds, E. M. 1980. Aetiology of pre-eclampsia: a review. *J. R. Soc. Med.*, 73:871-875.

Tallarigo, L., O. Giampietro, G. Penno, R. Miccoli, G. Gregori, and R. Navalesi. 1986. Relation of glucose tolerance to complications of pregnancy in nondiabetic women. *N. Engl. J. Med.*, 315:989-992 (and ensuing correspondence in *N. Engl. J. Med.*, 316:1343-1346).

Talmadge, K., N. C. Vamvakopoulos, and J. C. Fiddes. 1984. Evolution of the genes for the β subunits of human chorionic gonadotropin and luteinizing hormone. *Nature*, 307:37-40.

Thompson, J., W. Zimmermann, P. Osthus-Bugat, C. Schleussner, A.-M. Eades-Perner, S. Barnert, S. von Kleist, T. Willcocks, I. Craig, K. Tynan, A. Olsen, and H. Mohrenweiser. 1992. Long-range chromosomal mapping of the carcinoembryonic antigen (CEA) gene family cluster. *Genomics*, 12:761-772.

Thomson, A. M., W. Z. Billewicz, and F. E. Hytten. 1969. The weight of the placenta in relation to birthweight. *J. Obstet. Gynaecol. Br. Commonw.*, 76:865-872.

Thorbert, G., P. Alm, A. B. Björkland, C. Owman, and N.-O. Sjöberg. 1979. Adrenergic innervation of the human uterus. Disappearance of the transmitter and transmitter-forming enzymes during pregnancy. *Am. J. Obstet. Gynecol.*, 135:223-229.

Trivers, R. L. 1974. Parent-offspring conflict. *Am. Zool.*, 14:249-264.

Tsukimori, K., H. Maeda, M. Shingu, T. Koyanagi, M. Nobunaga, and H. Nakano. 1992. The possible role of endothelial cells in hypertensive disorders during pregnancy. *Obstet. Gynecol.*, 80:229-233.

Tullner, W. W. 1974. Comparative aspects of primate chorionic gonadotropins. *Contrib. Primatol.*, 3:235-257.

Turner, W. 1876a. Some general observations on the placenta, with especial reference to the theory of evolution. *J. Anat. Physiol.*, 11:33-53.

———. 1876b. *Lectures on the Comparative Anatomy of the Placenta.* Adam and Charles Black, Edinburgh. (An abridged version of these lectures appeared as: Turner, W. 1875. On the structure of the diffused, the polycotyledonary and the zonary forms of placenta. *J. Anat. Physiol.*, 10:127-177.)

Tyson, J. E., K. L. Austin, and J. W. Farinholt. 1971. Prolonged nutritional deprivation in pregnancy: changes in human chorionic somatomammotropin and growth hormone secretion. *Am. J. Obstet. Gynecol.*, 109:1080-1082.

Tyson, J. E., K. Austin, J. Farinholt, and J. Fiedler. 1976. Endocrine-metabolic response to acute starvation in human gestation. *Am. J. Obstet. Gynecol.*, 125:1073-1084.

Vaquer, S., A. de la Hera, J. Jordá, C. Martínez-A., M. Escudero, and M. Alvarez-Mon. 1987. Diminishing natural killer activity in pregnancy: modulation by interleukin 2 and interferon γ. *Scand. J. Immunol.*, 26:691-698.

Van Assche, F. A., L. Aerts, and F. de Prins. 1978. A morphological study of the endocrine pancreas in human pregnancy. *Br. J. Obstet. Gynaecol.*, 85:818-820.

Viljoen, D., and R. Ramesar. 1992. Evidence for paternal imprinting in familial Beckwith-Wiedemann syndrome. *J. Med. Genet.*, 29:221-225.

Wagstaff, J., J. H. M. Knoll, J. Fleming, E. F. Kirkness, A. Martin-Gallardo, F. Greenberg, J. M. Graham, J. Menninger, D. Ward, J. C. Venler, and M. Lalande. 1991. Localization of the gene encoding the $GABA_A$ receptor β_3 subunit to the Angelman/Prader-Willi region of human chromosome 15. *Am. J. Hum. Genet.*, 49:330-337.

Waites, G. T., S. C. Bell, R. A. Walker, and P. L. Wood. 1990. Immunohistological distribution of the secretory endometrial protein, 'pregnancy-associated endometrial α_2-globulin', a glycosylated β-lactoglobulin homologue, in the human fetus and adult employing monoclonal antibodies. *Hum. Reprod. (Oxf.)*, 5:105-111.

Waites, G. T., R. F. L. James, and S. C. Bell. 1988. Immunohistological localization of the human endometrial secretory protein pregnancy-associated endometrial α_1-globulin, an insulin-like growth factor binding protein, during the menstrual cycle. *J. Clin. Endocrinol. & Metab.*, 67:1100-1104.

Wake, N., N. Takagi, and M. Sasaki. 1978. Androgenesis as a cause of hyatidiform mole. *J. Natl. Cancer Inst.*, 60:51-53.

Walker, W. H., S. L. Fitzpatrick, H. A. Barrera-Saldaña, D. Reséndez-Pérez, and G. F. Saunders. 1991. The human placental lactogen genes: structure, function, evolution, and transcriptional regulation. *Endocr. Rev.*, 12:316-328.

Wallenburg, H. C. S. 1988. The placenta in pregnancy hypertension. In P. C. Rubin (ed.), *Handbook of Hypertension, Volume 10: Hypertension in Pregnancy*, pp. 66-101. Elsevier, Amsterdam.

Wang, H., S. J. Segal, and S. S. Koide. 1988. Purification and characterization of an incompletely glycosylated form of human chorionic gonadotropin from human placenta. *Endocrinology*, 123:795-803.

Wang, H. S., J. Lim, J. English, L. Irvine, and T. Chard. 1991. The concentration of insulin-like growth factor-1 and insulin-like growth factor-binding protein-1 in human umbilical cord serum at delivery: relation to fetal weight. *J. Endocrinol.*, 129:459-464.

Weigel, M. M., and R. M. Weigel. 1989. Nausea and vomiting of early pregnancy and pregnancy outcome. An epidemiological study. *Br. J. Obstet. Gynaecol.*, 96:1304-1311.

Weigel, R. M., and M. M. Weigel. 1989. Nausea and vomiting of early pregnancy and pregnancy outcome. A meta-analytical review. *Br. J. Obstet. Gynaecol.*, 96:1312-1318.

Weksberg, R., I. Teshima, B. R. G. Williams, C. R. Greenberg, S. M. Pueschel, J. E. Chernos, S. B. Fowlow, E. Hoyme, I. J. Anderson, D. A. H. Whiteman, N. Fisher, and J. Squire. 1993. Molecular characterization of cytogenetic alterations associated with the Beckwith-Wiedemann syndrome (BWS) phenotype refines the localization and suggests the gene for BWS is imprinted. *Hum. Mol. Genet.*, 2:549-556.

Wessman, M., K. Ylinen, and S. Knuutila. 1992. Fetal granulocytes in maternal venous blood detected by in situ hybridization. *Prenatal. Diagn.*, 12:993-1000.

Whitsett, J. A., C. L. Johnson, and K. Hawkins. 1979. Differences in localization of insulin receptors and adenylate cyclase in the human placenta. *Am. J. Obstet. Gynecol.*, 133:204-207.

Williams, J. W. 1931. Regeneration of the uterine mucosa after delivery, with especial reference to the placental site. *Am. J. Obstet. Gynecol.*, 22: 664-696. (This study appears to have used uteri from involuntary sterilizations removed at timed stages after delivery.)

Wilson, R., J. H. McKillop, M. MacLean, J. J. Walker, W. D. Fraser, C. Gray, F. Dryburgh, and J. A. Thomson. 1992. Thyroid function tests are rarely abnormal in patients with severe hyperemesis gravidarum. *Clin. Endocrinol.*, 37: 331-334.

Wurzel, J. M., J. S. Parks, J. E. Herd, and P. V. Nielsen. 1982. A gene deletion is responsible for absence of human chorionic somatomammotropin. *DNA (NY)*, 1:251-257.

Wynn, R. M. 1967. Fetomaternal cellular relations in the human basal plate: an ultrastructural study of the placenta. *Am. J. Obstet. Gynecol.*, 97:832-850.

———. 1974. Ultrastructural development of human decidua. *Am. J. Obstet. Gynecol.*, 118:652-670.

———. 1989. The human endometrium. Cyclic and gestational changes. In R. M. Wynn and W. P. Jollie (eds.), *Biology of the Uterus*, 2nd ed., pp. 289-331. Plenum Press, New York.

Yeh, I.-T., and R. J. Kurman. 1989. Functional and morphologic expression of trophoblast. *Lab. Invest.*, 61:1-4.

Zarcone, D., O. Viale, G. Cerruti, C. Tenca, W. Malorni, G. Arancia, F. Iosi, R. Galandrini, A. Velardi, A. Moretta, and C. E. Grossi. 1992. Antibodies to adhesion molecules inhibit the lytic function of MHC-unrestricted cytotoxic cells by preventing their activation. *Cell. Immunol.*, 143:389-404.

Zemel, S., M. S. Bartolomei, and S. M. Tilghman. 1992. Physical linkage of two mammalian imprinted genes, H19 and insulin-like growth factor 2. *Nature Genet.*, 2:61-65.

Zhang, Y., and B. Tycko. 1992. Monoallelic expression of the human H19 gene. *Nature Genet.*, 1:40-44.

Zhu, H. H., J. R. Huang, J. Mazela, J. Elias, and L. Tseng. 1992. Progestin stimulates the biosynthesis of fibronectin mRNA in human endometrial stromal cells. *Hum. Reprod. (Oxf.)*, 7:141-146.

Ziegler, E. E., A. M. O'Donnell, S. E. Nelson, and S. J. Fomon. 1976. Body composition of the reference fetus. *Growth*, 40:329-341.

Zini, J.-M., S. C. Murray, C. H. Graham, P. K. Lala, K. Karikó, E. S. Barnathan, A. Mazar, J. Henkin, D. B. Cines, and K. R. McCrae. 1992. Characterization of urokinase receptor expression by human placental trophoblasts. *Blood*, 79:2917-2929.