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Some Evolutionary Aspects of the Human Placenta

by

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Egg-laying as a means of reproduction presents many hazards for land-bound creatures. It is a system which has been abandoned by all mammals except for two primitive monotremes, the duckbill and the porcupine ant-eater. The yolk-sac does persist in most placentates but only as a paraplacental auxiliary structure. Viviparity was obviously the system most conducive to the survival of mammalian species, and this required some form of placentation. The achievement of placentation must have required innumerable trials and errors, and the mistakes undoubtedly led to the extinction of as many species.

What were some of the problems encountered by Nature in evolving the present system of reproduction possessed by man? How did Nature (or God, if you prefer) go about designing a placenta for Homo sapiens? And what are the attendant disadvantages which have arisen from the current solution?

The lowest form of an existing vertebrate is the hagfish, a sucking cyclostome that has no thymus or reticulo-endothelial system. Just above this creature is the lamprey eel, which does have a thymus. From thence on, all animals possessed a reticulo-endothelial system which rendered them capable of rejecting homografts (as well as combating certain types of infections). I heard an immunologist state that from his standpoint, human pregnancy is an impossibility! In as much as the placenta is genetically a homograft, Nature was faced with a preexisting and almost insurmountable problem. She solved this problem by inventing the syncytiotrophoblast, to me the most mysterious cell of any mammalian tissue. It has now been established that the cytotrophoblast (Lañghans' cell) gives birth to this tissue, but at that point any resemblance of offspring to parent ceases. Researches of the last two or three years have strongly supported the concept that the syncytium lacks the antigenicity necessary to provoke the rejection of a graft. Since, throughout the mammalian deciduate placentates, such a syncytium is interposed between the fetus and the mother pregnancy could now proceed beyond the few days of grace when rejection would normally occur. There are some species such as the pig, cow and horse in which there is no true syncytium, but they do not have deciduate placentas and there is no invasion of maternal tissues.

A second serious problem was also solved by the invention of the syncytiotrophoblast. To develop a suitable placenta for the primate, the trophoblast had to establish contact with the maternal vessels, and to do this, it obviously had to invade the maternal tissues. I can imagine that in many evolutionary trials, some variant species became extinct because it was killed by the invasion of a new type of trophoblast. But the syncytiotrophoblast is able to invade until it establishes adequate contact with the maternal circulation, and then it ceases to invade. The precise explantation for this is not well understood, although Boving[1] believes that the invasion is due to a "pile up" of bicarbonate resulting from a deficiency of respiratory exchange; that when this bicarbonate escapes into the endometrium, it meets with carbonic anhydrase (which has been stimulated by progesterone) and deposits carbonate. This increases the local pH to around 9, which causes disintegration of the endometrial cells. When the maternal capillaries are eroded, the blood stream carries away the respiratory products and invasion ceases. This may be true, but it does not explain why the millions of syncytial buds or knots that are constantly deported to the maternal lungs and elsewhere do not invade other tissues. I would answer this by saying that syncytium cannot reproduce. **No one has ever seen a mitotic figure in the syncytiotrophoblastic nucleus of any species.** In this respect, the tissue differs from cancer. It was

even suggested recently (by Galton), that the syncytium might be haploid, and contain only 23 maternal chromosomes; but Quinlivan[2], working in our laboratory, measured the DNA content of human syncytial nuclei and found it to be the same as diploid cells.

An alternate explantation for the limitation of invasiveness of trophoblast might be that the maternal tissues "throw up" an immunologic line of defense. Recently, we produced tolerance in rabbits by injecting the fetuses **in utero** with lymphocytes of the father. Many of them developed runt disease and died (because the graft rejected the host) but a few survived. One female bunny received skin from her father and it "took" for six weeks, proving that she was tolerant to her father's tissues. We then mated the daughter to the father, and what happened? She had a completely normal pregnancy with normal placenta. Thus it could hardly be an immune defense mechanism of the host which prevents an invasion of the host by the trophoblast.

The next major problem that Nature attempted to solve was the prolongation of pregnancy beyond the estrus cycle. The forerunners of the wolf, weasel, shrew, squirrel, bear and possibly all mammals existed as marsupials before the invention of the placenta. On the continent of Australia, this situation persisted much longer than on other land masses, because the entire continent was at one time populated only by marsupials, all of whom aborted embryos. A few of these species managed to survive. The largest of these, the giant grey kangaroo, standing five feet high, aborts an undeveloped embryo measuring 20 to 30 mm. in length. The mother smooths down a pathway of hair from her cloaca and the embryo bumbles along this spittle trial and finds its way into her pouch, where a normal teat exists. The mouth of the embryo attaches to the mamilla and remains there for 7 or 8 months. This strikes me as being a rather hazardous method of reproduction (though one which has distinct possibilities for birth control) and I wonder at the fact that kangaroos and 'possums are still with us.

The earliest placentas may have been aborted in a similar fashion, and it was not until a mutant trophoblastic or endometrial cell arose with the capability of secreting a luteotrophic hormone that the problem was solved. This protein hormone permitted the corpus luteum of the ovary to survive and remain functional. Progesterone is obviously the key hormone for both the implantation and the maintenance of pregnancy throughout the placentate mammals. For most mammals with relatively short gestation periods, the corpus luteum of pregnancy sufficed for the prolongation of pregnancy, and the intricate mechanisms which determine its life span also controlled parturition. For reasons which I do not understand, any given corpus luteum in mammals rarely (if ever) remains functional for more than two or three months. Perhaps it is the presence of the luteinizing hormone of the pituitary which causes its downfall (as in the rat). Perhaps it is the presence of the uterus, as in the guinea pig, sheep, pig and cow. In the guinea pig, for example, hysterectomy on day 5 of the luteal cycle permits the corpus luteum to remain functional for 8 months or longer.

The mare solved her problem by developing an endometrial cell which produced a luteotrophin ("pregnant mare serum"), which in turn produced successive crops of new corpora lutea during pregnancy. A similar situation arose in the elephant, which has the longest known gestation period (22 months). I see no compelling reason why this system would not work for primates.

Be that as it may, Homo sapiens discovered an alternate technic: The syncytiotrophoblast developed the potential of synthesizing both estrogen and progesterone and thus the ovaries became dispensible after the first two or three months.

Now we come to a very critical problem in the evolution of man; one which had to be solved by compromise. I must refer to orthogenesis, which is the inherent tendency of a species to persevere along certain specialized lines even though such specialization may lead to its ultimate extinction. In some respects, man is primitive—his teeth, five fingers and toes, the simple stomach, his small face, the simple male genitalia. It is the development of his brain which sets him apart. The ratio of the cerebral cortex to the midbrain in man is 170; in the chimpanzee 49, the monkey 38, the rabbit 5 and the hedgehog 0.8. The lower the ratio, the greater is the creature governed by instinct alone, whereas in man instinct may be completely suppressed by reason (except after cocktail parties).

Kovacs[3], of Budapest, has marshalled evidence to show that human pregnancy should last 21 months. It is not until the human infant is one year of extrauterine age that it has equalled the maturity of any other primate, or indeed (with the exception of marsupials) with the newborn of any other species. This is true whether one studies neuromuscular ability, contact with the environment, thermoregulation, digestive abi-

lity, ossification centres, ratio of body parts, enzyme development or any other parameter. In other words, human babies are all born one year prematurely and must have a high degree of maternal care in order to survive. Repeatedly-no one knows how many times—Nature tried to design a placenta and a uterus which would prolong pregnancy in the human species for more than 9 lunar months. (Lest one believes that pregnancy lasts 10 luar months, I must point out that a lunar cycle is 29.53 days, and human gestation from conception to birth lasts 9 lunar cycles). Every time Nature tried, she was defeated by cephalopelvic disproportion. Orthogenesis, on the one hand, was enlarging our skulls to accommodate our brains; whereas the assumption of an upright position placed a marked curve in the birth canal and limited the pelvic capacity. Several tricks were tried, but most were unsuccessful. One device that did help to some extent was the development at puberty of the gynecoid pelvis in the human female, as opposed to the android type. In other species, there is little difference between male and female pelves.

The struggle to solve this problem still goes on. We encounter women who are habitually postmature and who may give rise to healthy giant newborns. If we preserve this genetic line by repeated caesarean sections, we may ultimately breed a variant species with a longer gestation. We also encounter women who habitually deliver prematurely, but this may be due to a variety of causes, such as cervical incompetence or some atavistic anomaly of the uterus. Curiously enough, there is some sort of lunar cycle which persists throughout human pregnancy. Both abortion and abruption occur with a peak frequency at monthly intervals, and there may be cyclic changes in capillary fragility during gestation, just as there is in the menstrual cycle. Such rhythms must be governed by the hypothalamus, rather than by endocrine organs **per se,** and may be a reflection of certain mysterious biologic cycles which seem to be evident throughout the animal kingdom.

A series of adaptations arose, which together, preserved our species from extinction. For primates, she fused the Mullerian ducts and created a cervix to retain the conceptus. For most individuals, she reduced the litter size to one. She created a placenta and a uterus and a fetus which, working in harmony, resulted in a coordinated uterine activity and parturition **just before the fetal head became too large to pass through the bony pelvis.**

Now, in the last few million years, we are approaching the crux of a dilemma. Given a species with a small, single uterus, a large fetus at term in a relatively small elliptoid organ; a creature that insists upon shifting frequently from a supine to an upright position; one which must terminate its pregnancy prematurely for mechanical reasons, yet support growth and development until that time; how could a placenta evolve which would permit the survival of such a species?

Long before Dr. Fick, Nature was aware of Fick's equation, which states that the rate of exchange across a membrane is proportional to the area, to the chemical gradient and time, and inversely proportional to the thickness of the membrane.

A diffuse, labyrinthine placenta was tried and worked successfully for such primates as the lemur and sloth but must have led to complications in primitive man. Occasionally, a diffuse villous placenta occurs today, but is associated with placenta praevia and haemorrhage. A discoid placenta worked well, but it had to acquire a villous structure in order to pack 160 square feet of surface into a 15 to 20 cm. disc. A succenturiate lobe was tried in order to double the area, and in the macacus monkey this is the rule, and apparently works well. Some women try it today, but it leads to a higher frequency of third stage haemorrhage and perhaps was discarded for that reason.

The placental membrane could consist of any number of layers from one to six. Nature must have found that only one layer of trophoblast could be interposed between maternal blood and fetal capillaries to permit enough orygen to diffuse across for the heavy demands of a seven pound human fetus. This also had the advantage of permitting the transfer of maternal antibodies to the fetus. The six-layered placenta of the pig will not permit such a transfer, and unless piglets obtain their antibodies from colostrum in the first day or so, they routinely die of infection. On the other hand, the thin hemochorial membrane is more subject to breaks, leading to intervillous thrombi and to our problems with isoimmunization. Not only do breaks occur in the barrier, but breaks occur in the thin walled terminal sacs of the decidual arteries, resulting in abruption. The open venous exits in the decidual plate invite the entrance of thromboplastic proteins or even amniotic fluid into the maternal circulation, leading to afibrinogenemia or to amniotic fluid embolism. The large intervillous space resulted in a relatively slow circulation of

maternal blood, which permitted an extension of the time needed for diffusion. To cope with the highly complex coagulation system of the blood, the syncytium had to develop an anticoagulant surface. As yet, this is incompletely solved, because fibrin deposition and intervillous coagulation are the rule rather than the exception. Thousands of intrauterine deaths occur yearly from these changes which lead to the situation we call "placental insufficiency."

Thus a type of placenta evolved which was designed to produce a maximal diffusion within a compact organ; but this was not good enough for the **nutritional** requirements of the growing fetus. The syncytiotrophoblast had yet another attribute to develop—the power to select certain biochemical materials, concentrate and then release them into the fetal blood **against** the chemical gradient. Active transfer mechanisms were developed for glucose, the natural amino acids, thiamine, pyridoxine, any many other substances known to be important for the rapid growth of tissues. In my opinion, **these are the systems which control the rate of growth of the fetus.** When the concentrating power of the placenta is lost (as it is in some of the hypertensive complications of pregnancy), the rate of fetal growth is slowed markedly. In some instances of chronic renal hypertension, a puny 1800 gram fetus may be born at term.

At this point, I would like to introduce a theory, realizing that propounding hypotheses is currently unpopular in scientific circles. I would defend the viewpoint, however, that the interpretation of available data assumes an importance not subservient to the production of a new fact.

The concept is concerned with the adaptation of the trophoblast of the human placenta to an unfavourable environment, such as a reduced circulation of maternal blood through the intervillous space, leading to a low oxygen tension and a poor exchange of water and its solutes. To personify and utilize teleology for a moment, what would you do if you were a fetal tissue—the human placenta—interested primarily in saving fetal life? You have already dilated your own vessels to permit the maximal flow of fetal blood. You are already producing the maximal amount of histamine to keep the vascular channels open. You have already grown to the maximal anatomic surface area possible. You cannot raise the chemical gradient, because the host is being uncooperative. There are only three remaining possibilities: You could increase the head of maternal perfusion pressure; you could reduce the maternal plasma protein level to permit a better distribution of water and its solutes in favour of the fetus; or you could reduce the thickness of your barrier to almost infinite thinness to encourage more rapid diffusion.

The hypothesis may be summarized in six statements:

1. A low oxygen tension, secondary to an impaired circulation of maternal blood, leads to a progressive thinning of the placental barrier. This statement can be supported by histologic evidence.

2. This thinning, even to the appearance of "naked villi" under the light microscope, has been called "degeneration or ageing of the syncytiotrophoblast." Rather than postulate degeneration, perhaps the syncytium thins out by the process of forming multinucleated buds or knots which then pinch off and become deported into the maternal circulation without causing a break in the outer membrane of this gigantic cell. Such a process, of course, would serve to reduce the ability of the syncytium to perform active transfer of nutriments or to secrete estrogen and progesterone, but this sacrifices a long term objective for the more immediate purpose of supporting life by permitting more rapid oxygen transfer.

3. In response to this loss of syncytiotrophoblast, the cytotrophoblast proliferates and attempts to repair the injury by producing more syncytium. (Remember that the syncytium has no ability to reproduce itself). This proliferation of the cytotrophoblast can be observed in cases of erythroblastosis, nephritis, preeclampsia and other diseases resulting in placental injury.

4. If the cytotrophoblast is the source of chorionic gonadotrophin, and the syncytium is the source of estrogen and progesterone, then this entire process should be reflected clinically by a rise in the excretion of chorionic gonadotrophin and a fall in the excretion of estriol and pregnanediol. This is exactly what we observe in the hypertensive complications of pregnancy, severe diabetes or severe erythroblastosis. Indeed, the measurement of the urinary excretion of estrogens or of pregnanediol has been proposed as an estimate of fetal jeopardy.

5. A further extension of this same process may induce the placenta to release some material which is able to raise the maternal blood pressure and even reduce the concentration of maternal plasma albumin or increase its water content or both. When this happens, we have a combination of maternal symptoms which bear the label preeclampsia.

6. The progressive loss of syncytial substance leads to an impairment of active transfer of amino acids, and in all likelihood of other nutriments requiring active transport. This results in a retardation of intrauterine growth, a well known clinical phenomenon. The reduction of steroid secretion may also lead to early labor, because under conditions of so-called placental insufficiency, premature labor is very common. When all of these processes designed to cope with an impaired maternal circulation to the placenta fail, intrauterine death occurs.

To me, the attractiveness of these hypothesis lies in the relating of a variety of clinical facts to a single physiologic event.

Curiously enough, Nature has discovered a solution for the placenta of monkey and of man (but of no other species known) for some sort of problems which we have not yet discovered. The human and monkey trophoblast elaborates an aminopeptidase—variously known as Pitocinase, oxytocinase, vasopressinase or cystine amninopeptidase—which appears in the plasma of pregnant women in steadily increasing concentrations as gestation progresses. It does not exist in measurable quantities in men or in nonpregnant women. Because it can inactivate the posterior pituitary hormones with considerable rapidity, we are inclined to ascribe some purpose to this enzyme that is related to these particular hormones. But let us pause for a moment of reflection. Just because we have used such familiar substrates as oxytocin and vasopressin to demonstrate this enzyme's activity, does this mean that the "purpose" of the enzyme is to destroy these hormones? Could it not be that there are structurally similar polypeptides concerned in some way with human reproduction that we have not yet discovered? Could it be, for example, that the undiscovered peptides are involved in the causation of preeclampsia and eclampsia—diseases which only occur spontaneously in those primates known to possess this particular enzyme?

At this point, I would not know whether you have concluded that the process of evolution has served us well in the design of our placenta or not. The mere fact that the "population explosion" is considered to be the number two problem of the world today is testimony favouring our present system of reproduction. The number one problem obviously concerns the human brain. But the phylogenetic development of the human placenta has not proceeded without serious attendant disadvantages. I have already alluded to these, but let me recapitulate.

The anatomic development of the human placenta in terms of its invasion and attachment has led to placenta praevia, abruption or abortion, placenta succenturiata or circumvallata and choriocarcinoma. The thin, haemochorial layer has led to isoimmunization and haematomas. The utero-placental circulation has led to true infarction, fibrin deposition, afibrinogenamia and embolism. Functional aberrations have led to intrauterine retardation of growth, preeclampsia and eclampsia, prematurity and postmaturity.

I would like to quote from an article which Grosser[4] wrote for the Lancet in 1933: "No doubt the human type of placentation is to be considered as a product of evolution and even as the terminal production of a phylogenetic line, not to be continued or even to be surpassed. But such extremes have always been, in phylogeny, dangerous to their bearers.....In geologic times, many species have become extinct, and always they were the highest and the mightiest existing. Always some organ or organ system developed in an excessive way. Rather than adaptation, one must admit orthogenesis—the inherent tendency of organisms to persevere along a line of development that the species has entered upon.....In man, orthogenesis has led to the development of two very highly specialized organs, the brain and the placenta. One or the other will ultimately lead to the extinction of man."

In 1933, Grosser implied that it would be the placenta which would lead to our extinction, but in 1963, the combination of the fusion bomb and inept politics would lead me to wager on the human brain. Should we ever achieve "one world" in the political and economic sense, then man could concentrate more on problem of successful, controlled human reproduction.

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