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Biparental origin of the chromosome set is required for a developing human being

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Abstract

Conception sometimes results in products that are not capable of developing into an embryo and fetus. This group, designated with the term gestational trophoblastic neoplasia, comprises the benign hydatidiform mole, the invasive mole (chorioadenoma destruens) and the frankly malignant variety, choriocarcinoma. Another type of atypical oocyte activation occurs in parthenogenesis. In the human, two types of tumors, dermoid cysts and teratomas, can result from this process. The authors of this paper aim to elucidate the mechanisms how these abnormal growths ensue and provide explanations why they cannot be regarded as human individuals or human beings. They conclude that it is not the exact number of chromosomes that is required for a form of human life to become a human being but rather the biparental origin of the chromosome set.

It is obvious that, apart from the future perspectives of reproductive cloning, all forms of *human life* begin with conception. But does conception always result in a *developing human being?* The answer is certainly no. Careful studies in women attempting pregnancy have shown that implantation fails in about 30% of cases and in another 30%, human chorionic gonadotropin (hCG) can transiently be detected in the urine of women who would otherwise be unaware that they had conceived and miscarried *(1)*. One could argue that there is a developing human being in these cases that simply failed to develop but in fact, most of these embryos have some type of chromosomal abnormalities that would impede their development to term.

Conception sometimes results in a special form of tumors, which belong to the group designated with the term gestational trophoblastic neoplasia. This group comprises the benign hydatidiform mole (Figure 1), the invasive mole (chorioadenoma destruens) (Figure 2), and the frankly malignant variety, choriocarcinoma (Figure 3). What these tumors have in common is their origin: they are derived from cytotrophoblast and syncytiotrophoblast cells, which normally would form the outer layer of the early developing blastocyst, giving later rise to chorionic villi of the placenta.

The majority of hydatidiform moles are »complete« moles, in which no traces of a developing embryo can be found. In about 95% of cases, cells of these tumors have a 46,XX karyotype, in which both X chromosomes are paternally derived (Figure 4). These cells result from fertilization of an oocyte by a single sperm in a way that the nucleus of the

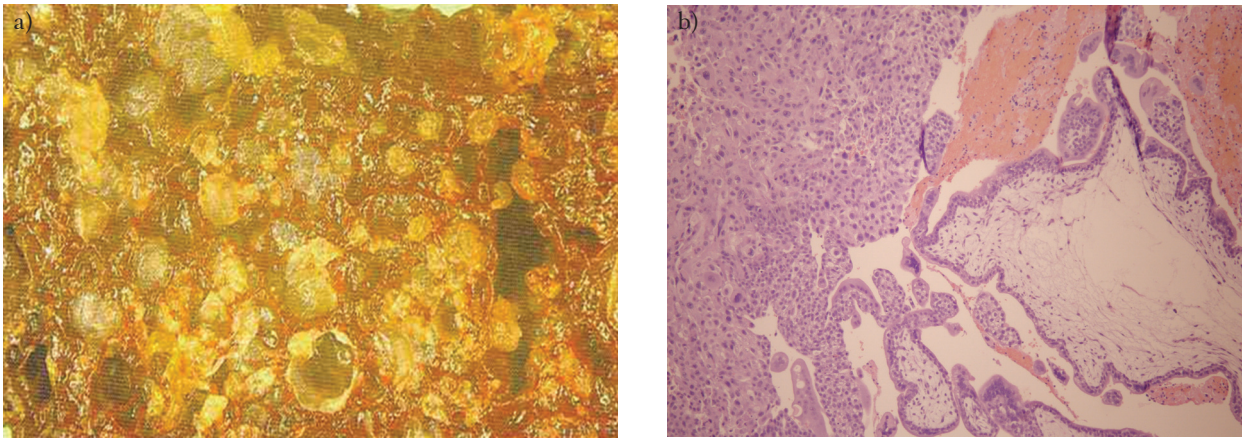


Figure 1. *Macroscopic (A) and microscopic (B) images of hydatidiform mole.*

oocyte degenerates and the chromosome set of the sperm (23,X) reduplicates. Alternatively, an empty egg may be fertilized by two sperm with two independent sets of 23,X or 23,Y. Therefore both karyotypes, 46,XX and 46,XY can ensue *(2)*.

Cells of the »incomplete« or partial mole usually carry a triploid karyotype, most often 69,XXY, which results from fertilization of a normal egg with two sperm cells or with a sperm carrying the unreduced paternal genome 46,XY. Unlike complete moles, these lesions present with a coexistent fetus, even though this embryo or fetus usually has a triploid karyotype as well and is defective. The triploidy leads to the death of the conceptus or, rarely, to fetal demise later in pregnancy. (There are some reports of infants born with triploid genomes but these children die within months *(3)*.).

Apart from the »fetal part« of partial moles, these tumors definitely cannot be regarded as human individuals or human beings as they lack a true human nature from the start and have no natural potential to begin human development. Complete moles lack the expression of all genes that are active only if inherited from the mother, i.e., imprinted if inherited from the father. Thus, a complete mole has a functionally incomplete genome, which radically changes its developmental trajectory. Growing into a tumor, it shows no sign of fetal tissue or any sign of cellular specialization. Therefore, the complete hydatidiform mole cannot be a unified organism *ab initio*. In other words, it cannot be an individual member of a particular biological species distinguished by a species-specific development that consists of an ordered sequence of appearance of differentiated cells and tissues *(4)*. On the other hand, only part of the embryo becomes a tumor in the case of partial mole, in the context of the abnormal development of the embryo/fetus. Thus, a partial mole is an embryo, albeit a disabled one *(4)*.

Another type of atypical oocyte activation occurs in a process known as parthenogenesis. In this case, eggs activate themselves without sperm. Although there are examples in the world of insects in which "workers" are produced by this process, mammalian parthenotes fail to develop into viable offspring. The absence of maternally imprinted molecules affects the parthenote as a whole since the involved genes regulate all cells of the developing blastocyst *(5)*. Experiments in the mouse have demonstrated that blastomeres are not identical as early as at

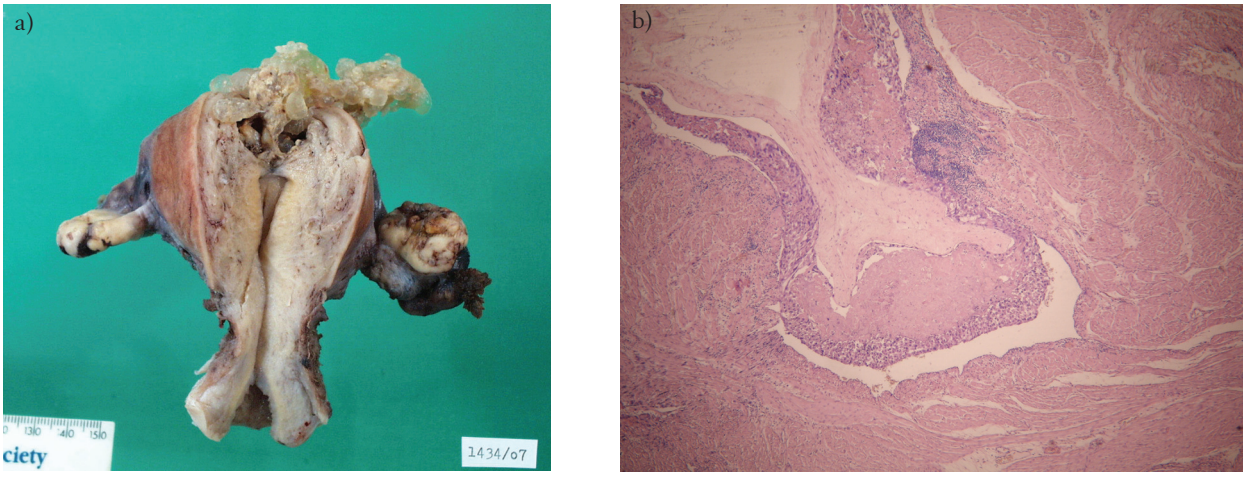
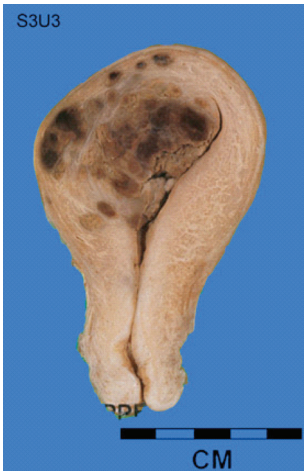


Figure 2. *Macroscopic (A) and microscopic (B) images of invasive mole (chorioadenoma destruens).*

a)



b)

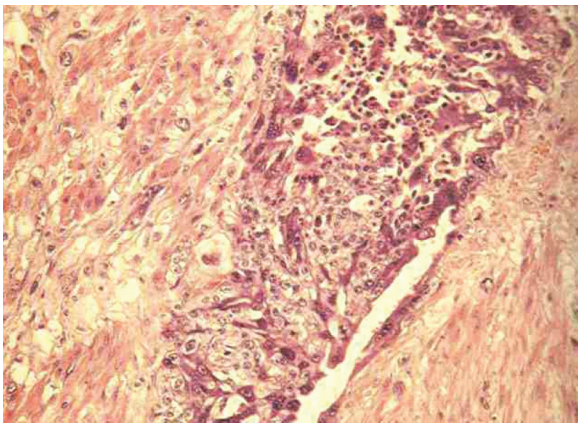


Figure 3. *Macroscopic (A) and microscopic (B) images of choriocarcinoma.*

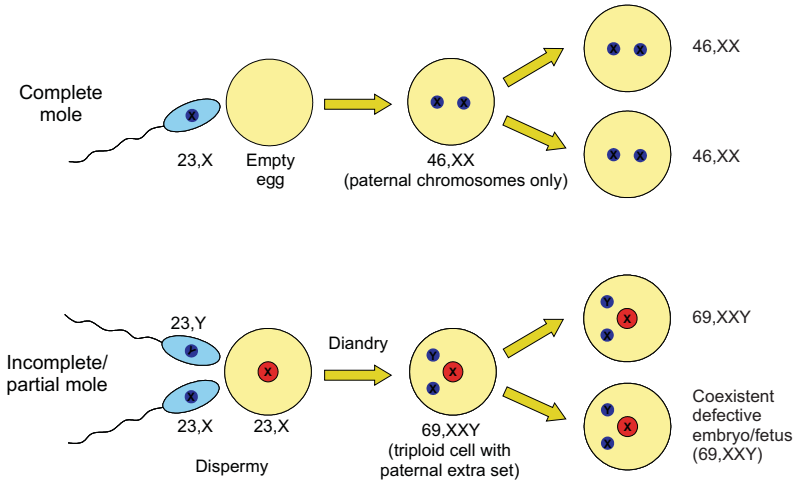


Figure 4. *Cytogenetic makeup of complete and incomplete (partial) hydatidiform moles.*

the two-cell stage of normal embryonic development. One of the two cells derived from a normal zygote divides ahead of the other, resulting in embryoblasts and trophoblasts, i.e., embryonic and extraembryonic cells and tissues, respectively *(6)*. In contrast, the two cells derived from the division of a mouse parthenote do not behave

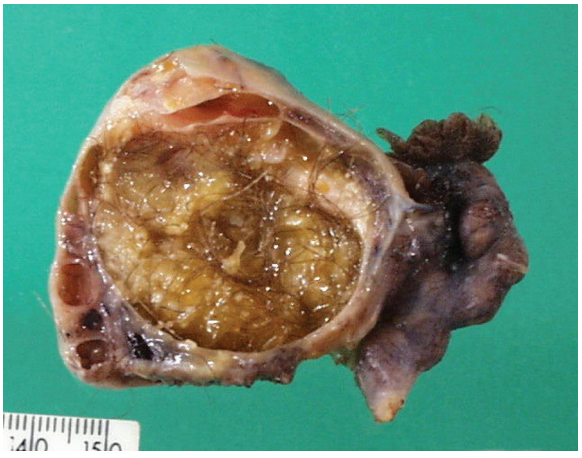


Figure 5. *Macroscopic image of a dermoid cyst.*

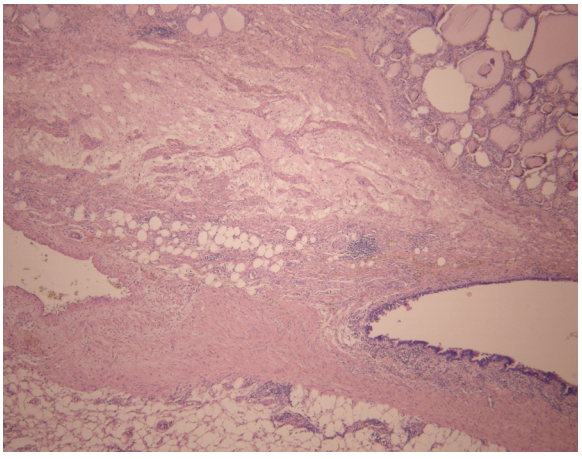


Figure 6. *Microscopic image of a benign ovarian teratoma.*

this way: the sister cell dividing first does not necessarily contribute to the formation of the embryo proper *(7)*. This demonstrates that the development of a parthenote already differs from that of a normal embryo, thus a parthenote cannot be regarded as an embryo.

There are several experimental procedures for parthenogenetic activation of the oocyte. Human oocytes activated in this manner have been shown to develop *in vitro* for five days, reaching the blastocyst stage, apparently indistinguishable at the gross morphological level from normal human embryos *(8)*. In the process of activation, the haploid oocyte duplicates its 23 chromosomes, which are thus all derived from the mother. Therefore, human parthenotes, unlike complete moles, lack the expression of all genes that are active only if inherited *paternally*. The fact that they can develop *in vitro* to the blastocyst stage is due to the presence of molecules expressed in the mother and inherited through the first mitotic divisions of the parthenote, which can compensate for defects in the genome of the »embryo«. However, normal development of parthenotes cannot proceed after a point where the store of these maternal molecules gets depleted *(4)*.

In the human, two types of growths have been demonstrated to result from parthenogenesis of oocytes. Dermoid cysts (Figure 5) are supposed to arise in unruptured ovarian follicles. The retained egg activates cell division on its own. The formation of the pathogenetically equivalent group of teratomas (Fig. 6) is not restricted to the ovaries but can occur in any part of the body where germ cells once passed on their way from the yolk sac to the sex cord during embryonic development. They are tumors that arise from a single germ cell after the first meiotic division *(9, 10)*. Thus, genetically, benign ovarian teratomas and dermoid cysts can be regarded as the female equivalent of the complete hydatidiform mole *(11)*.

Theoretically, these cells could be used as a source of stem cells but, for the very reason that mammalian parthenotes do not develop into viable offspring, it is currently not known with certainty whether stem cells carrying only maternally imprinted genes will behave the same way as embryonic stem cells. If yes, this would be an attractive alternative to the use of human embryos for obtaining stem cells *(12)*.

We cannot state, however, that these conceptions or tumors do not present a form of human life. To be able to resolve the apparent conflict between what constitutes human life and what makes up a human being, we need to review the definitions or, at least, the concepts that delineate each term.

Life has existed on Earth for approximately 3.5 billion years. It is transferred and not conceived in each new generation. If life is observed on the cellular level, then every form of life should be considered as a continuum. Human cells have existed continuously since the appearance of the first man but the cells of that individual were, after all, derived from the first cell ever.

It can be viewed that life begins when the chemical matter gives rise to an autonomous, self-regulating, and self-reproducing system. This system is an indivisible one – it forms its individuality. The human embryo and fetus gradually take on these characteristics.

The term 'human life' has several meanings. In line with the »cellular« definition above, every individual cell or organ of the human body constitutes human life but this is clearly not equivalent to being a 'human being'. At this point, 'organic or vegetative human life' is also not necessarily equivalent to 'potential personal human life'.

Defining personality, however, is very complex. If we try to use the definition, 'the state of existing as a thinking intelligent being', we may end up with inferring that personality increases *pro rata* with intelligence *(13)*. The description of personality as 'the individual as a whole with everything about the individual which makes him different from other people' is more acceptable. It is until approximately the 14th day after fertilization that monozygotic twins or chimeras can form. Therefore, genetic uniqueness and singleness coincide only after implantation. In fact, this seems to be the strongest reason why the preembryo (or whatever starts to develop during this period) cannot be regarded as an individual and a proof that the zygote cannot ontologically be a human being.

Also, if we accept that 'a human person cannot begin before the appropriate brain structures are developed that are capable of sustaining awareness,' this may help us understand why a grossly malformed fetus, even a live anencephalic fetus with only brain stem functions, would still be a human individual on one hand and why a hydatidiform mole or a teratoma would not on the other.

Now that we know the genetic makeup of moles, we are also able to resolve the question of personhood by the widely accepted notion that personhood is conferred by successful fertilization of the egg *(14):* it is exactly this point where the reproductive process is defective in the case of gestational trophoblastic disease. (Whether or not reproductive cloning by fusing somatic cell nuclei with enucleated oocytes would fit into this frame is beyond the scope of the present article.)

We can state thus with confidence that it is not the exact number of chromosomes that is required for a form of human life to become a human being (as in children born with Down's syndrome) but rather the biparental origin of the chromosome set.

In conclusion, it is indeed possible that conception can occur without the development of a human being. We hope this paper has elucidated the circumstances and the mechanisms when this occurs.

Note: Our theory was summarized in an Opinion Paper accepted for publication by the Journal of Perinatal Medicine.

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