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Origin, Nature and Significance of the "Embryoids" of Human Teratomas *

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With 23 Figures in the Text

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Introduction

The presence in human teratomas of structures which resemble early embryos represents a significant biological phenomenon which has not been well investigated, or generally accepted as such. For the study of these "embryoids" one needs to apply to their morphologic appearance, basic knowledge in human and experimental embryology including the concepts of embryonic induction and organization. The application of the embryologic knowledge to the study of the embryoids should result in a better understanding of their nature and biological significance and will produce valuable information regarding the origin, the nature and the evolution of human teratomas. We owe to ALFRED PEYRON, a French histologist, the discovery and the only systematic study available of the embryoid structures (boutons embryonaire) of human teratomas.

PEYRON presented his original discovery in a series of publications appearing in 1936 [PEYRON and LIMOUSIN (1, 2, 3)]. In many subsequent publications he described the morphology [PEYRON (1—9, 12); PEYRON, PATEL, POUMEAU-DELILLE and GOZLAND], the mode of division [PEYRON and LIMOUSIN (3, 4)], the presence of primordial germ cells (gonoblast) [PEYRON (10—12)], the presence of trophoblastic elements [PEYRON (7—9)] and the evolution [PEYRON (1)] of these structures. He considered them to be homologous to early stages of human embryos and to be the result of parthenogenesis (polyembryonic parthenogenesis) of the germ cells. Some of the embryoids he described are extraordinary examples of the degree of organization which these structures can achieve inside teratomas [PEYRON (2—4, 6)].

Since these original reports, many workers have recognized embryoid structures in human teratomas [DIXON and MOORE (2); EVANS; FRIEDMAN; GAILLARD (1, 2); MASSON; MELICOW; NICOD; SIMARD; TEILUM] and some excellent examples showing great embryoid organization have been described (EVANS; SIMARD). Recently, embryoid structures have been found in spontaneously occurring testicular teratomas in mice (STEVENS).

Our present knowledge about the embryoid structures of human teratomas is incomplete and their biological significance practically ignored. This is reflected in the fact that in leading text books and monographs dealing with human teratomas no mention is made of their occurrence [COLLINS and PUGH; WILLIS (1)] or only a brief notice is made of their presence as peculiar small structures, resembling embryos [DIXON and MOORE (1)]. No biological significance is attached to these structures by those who report their occurrence. Equally, the embryoid structures found in testicular teratomas in mice, although considered to be morphologically identical to early mouse embryos (STEVENS) have not had biological significance attached to them. STEVENS, concluded that embryoid structures in mouse teratomas "represent one of the many possible biological manifestations of the stem cell". But, in such explanation the basic problems remain unsolved since the interest rests in that

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particular biological property of the *stem cell* which is capable of producing embryoid structures with such a degree of organization.

The severe criticism which arose after PEYRON'S (MASSON) publications may explain that his numerous observations on embryoid structures have remained practically ignored outside of the French literature. The majority of his findings has neither been confirmed nor denied, and some of his opinions about the origin and nature of the embryoid structures are in need of revision.

The organization encountered in these structures in which an ectoderm, an endoderm, an amniotic cavity, a yolk-sac cavity and a primitive mesoderm, are arranged to constitute an embryoid surrounded by trophoblastic placenta, can not be explained simply as an occurrence without any biological significance. A systematic study of these highly organized structures of teratomas is needed, as well as an investigation of what *role* they may play in the biology of teratomas. Therefore the results of a systematic study of embryoid structures found in two human malignant teratomas are presented.

Material and Method

Case 1. 11 year old girl. Palpable mass in the cul-de-sac. Laparotomy: revealed a well encapsulated left ovarian tumor, 6 cm in diameter. No other tumor or metastasis was found at this time. Microscopically, the tumor was composed of areas of dysgerminoma (germ cell tumor), areas of immature embryonic tissue and areas of mature tissues (mature cystic teratoma). The patient was treated with radiotherapy and chemotherapy. Pregnancy tests were negative. Death after nine months. Autopsy: generalized malignancy. Microscopically, the tumor was composed of a single type of cell with an occasional large multinucleated cell similar to syncytiotrophoblast and had a reticular or lacunar appearance. This type of ovarian tumor has been described under different names by different workers. TEILUM called it mesoblastoma of extra-embryonic mesodermal origin. The tumor represents an example of a reticular embryonal carcinoma of FRIEDMAN, probably of trophoblastic origin, or a trophomesoblastoma of the French literature (MASSON) which is considered to be derived from both the trophoblast and the extra-embryonic mesoderm. In retrospect, a similar type of tissue was found in the primary ovarian tumor amoung the immature embryonic tissues.

Case 2. 19 year old male was admitted because of swelling and tenderness of both breasts and a mass in the left testicle of 3 weeks duration. 50% of the testicle was replaced by a hard nodule measuirng 2,5 × 3 cm. Microscopically, the tumor was composed of different kinds of tissue: areas of seminoma (germ cell tumor), areas of immature embryonic tissue (embryonal carcinoma and adenocarcinoma), areas of mature embryonic tissue (mature teratoma) and focal areas of trophoblastic cell proliferations (choriocarcinoma). Pregnancy tests were negative. About one month after the orchidectomy the patient was submitted to a bilateral inguinal and retroperitoneal lymph node dissection. One of the retroperitoneal lymph nodes was replaced by choriocarcinoma. The patient is under Actinomycin D. treatment.

These primary ovarian and testicular tumors were selected for study of embryoid structures for the following reasons: A. Both tumors, in spite of occurring in a female and in a male respectively were of similar nature. B. Each tumor was composed of tissues with different gradations in their development. On the one hand, tissues composed of pure germinomas (dysgerminoma and seminoma), and on the other hand, mature tissues of normal appearance and probably benign nature (skin, nervous tissue, ganglion cells, mucous glands, muscle, cartilage, etc.). Between these two extremes both tumors have poorly defined tissues of immature embryonic nature. And C. Both tumors represent an excellent material for the study of the relationship which may exist between these three types of tissues.

Observations

The main part of the description to follow is concerned with an analysis of the morphologic characteristics of the embryoid structures found in both tumors studied. There were no significant morphologic differences between the embryoid structures found in the female or in the male tumors. In view of that similarity, a general description of the morphologic characteristic of the embryoid from both tumors, will be presented regardless of their origin. However, the original teratoma from which the embryoids depicted in the figures came from will be properly acknowledged.

Table 1. *Classification of the "Embryoids" of human teratomas*

Complete embryoids		Imperfect embryoids		Amorpheous embryoids	
Developmental stage	Morula Blastocyst Embryoblastic Trophoblastic	Basic components	Amnio-ectodermic vesicle Yolk-endodermic vesicle Mesoderm ? Extra-embryonic mesoderm ? Mixed forms	Proliferating tissues	Ectoderm Endoderm Mesoderm Extra-embryonic mesoderm Trophoblast Mixed forms

For a better understanding and to facilitate their description the numerous embryoid structures encountered are classified into three categories (Table 1). The first category includes those structures showing morphologically complete embryoid organization. The embryoids of this category are divided in 4 stages according to their embryonic developmental age. The four stages are the "morula", the "blastocyst", the "embryoblastic" and the "trophoblastic" stages of embryoid development. The second category includes those incompletely or imperfectly formed embryoids which lack a sufficient organization to be classified in any of the stages of the first category of embryoids. These embryoids are identified by the principal elements of which they are composed. The third category includes an heterogeneous group of proliferating, amorphous embryonal tissues without embryoid organization. They are identified by their embryonic tissue component. The morphologic characteristics of the embryoids of each category is described below.

Complete embryoids

The morula stage of embryoid development (Fig. 1—3)[1] includes those structures ranging from earlier forms of cellular division to an easily identifiable morula-like group of cells. The earliest forms of cellular division may not be recognized easily because they lack a distinct morphological appearance which will differentiate them from the surrounding embryonal tissues. However, occassionally one encounters peculiar structures which may or may not represent the earliest forms of embryoids. Few of these peculiar morphologic structures composed of two large and identical cells resembling two blastomeres are depicted in Fig. 1. Fig. 2, shows a group of four large cells forming a spherical structure clearly separated from the other tissues. These earlier forms are encountered

[1] All photomicrographs are prepared from sections stained with hematoxylin and eosin.

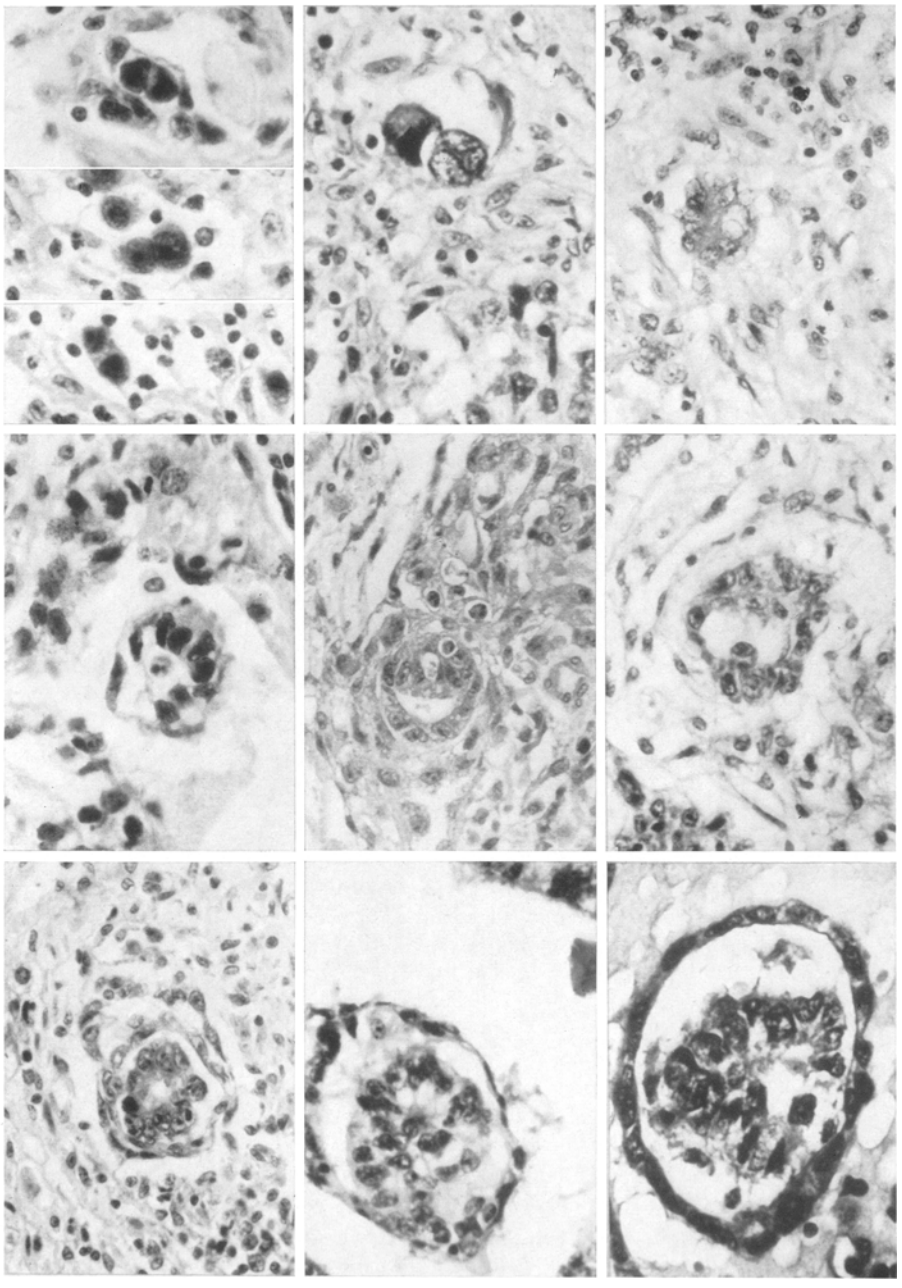


Fig. 1. Several cellular formations composed of two similar cells resembling two blastomeres. These cellular formations may represent the earliest forms of embryoids. ×275

Fig. 2. A four cell stage of an early morula-like embryoid. From the ovarian teratoma. ×250

Fig. 3. Morula-like embryoid surrounded by a clear watery stroma showing the beginning of the formation of a central cavity. From the ovarian teratoma. ×250

Fig. 4. Blastocyst-like embryoid encountered in a space filled with fluid (serum) showing the embryoblast and the trophoblastic wall. From the ovarian teratoma. ×250

Fig. 5. Early blastocyst-like embryoid showing clearly its components. From the testicular teratoma. ×250

Fig. 6. Blastocyst-like embryoid surrounded by clear watery stroma. From the testicular teratoma. ×250

at the periphery of the germinoma areas or in areas of embryonal tissues. More advanced forms of embryoids at the morula stage are easily recognized as spherical masses of cells. These morula-like embryoids are almost always separated from the surrounding tissue by a "clear and watery" stroma. This stroma shows a tendency to encircle the embryoid structure. This clear stroma became a distinctive characteristic of the embryoids in all developmental stages. An embryoid structure at a morula stage surrounded by a clear stroma is depicted in Fig. 3.

The blastocyst stage of embryoid development (Figs. 4—9) includes many variations of the same basic blastocyst-like structure. They show great variation in size, location and degree of development. The size of the embryoids depends on the amount of fluid accumulated in their cyst. The majority of them when found in tissues are surrounded by clear stroma which tends to encircle the structure (Figs. 6—7). A very common location of the blastocyst-like embryoids is in vascular spaces or in veins (Figs. 4, 8, 9).

The embryoid structures of this group resembles closely blastocysts of human or other mammals. They are composed of two portions: the wall of the blastocyst and the inner cell mass. The wall of the blastocyst is formed by large trophoblastic cells better appreciated in the embryoids encountered in vascular spaces (Figs. 4, 8, 9), also clearly seen in embryoids encountered in tissues (Figs. 5, 6, 7). The second component of the blastocyst consists of a small mass of cells, the embryoblast, attached to one pole of the blastocyst (Figs. 4—9). The cyst of these embryoids is filled with fluid in which floating cells with clear cytoplasm and stellar appearance are occasionally found (Figs. 8, 9). The most advanced embryoids of this group are characterized by the development of the embryoblast beyond the stage of the inner cell mass. The formation of another small cavity (amniotic cavity) within the inner cell mass, is the most common developmental phenomenon encountered (Figs. 8, 9).

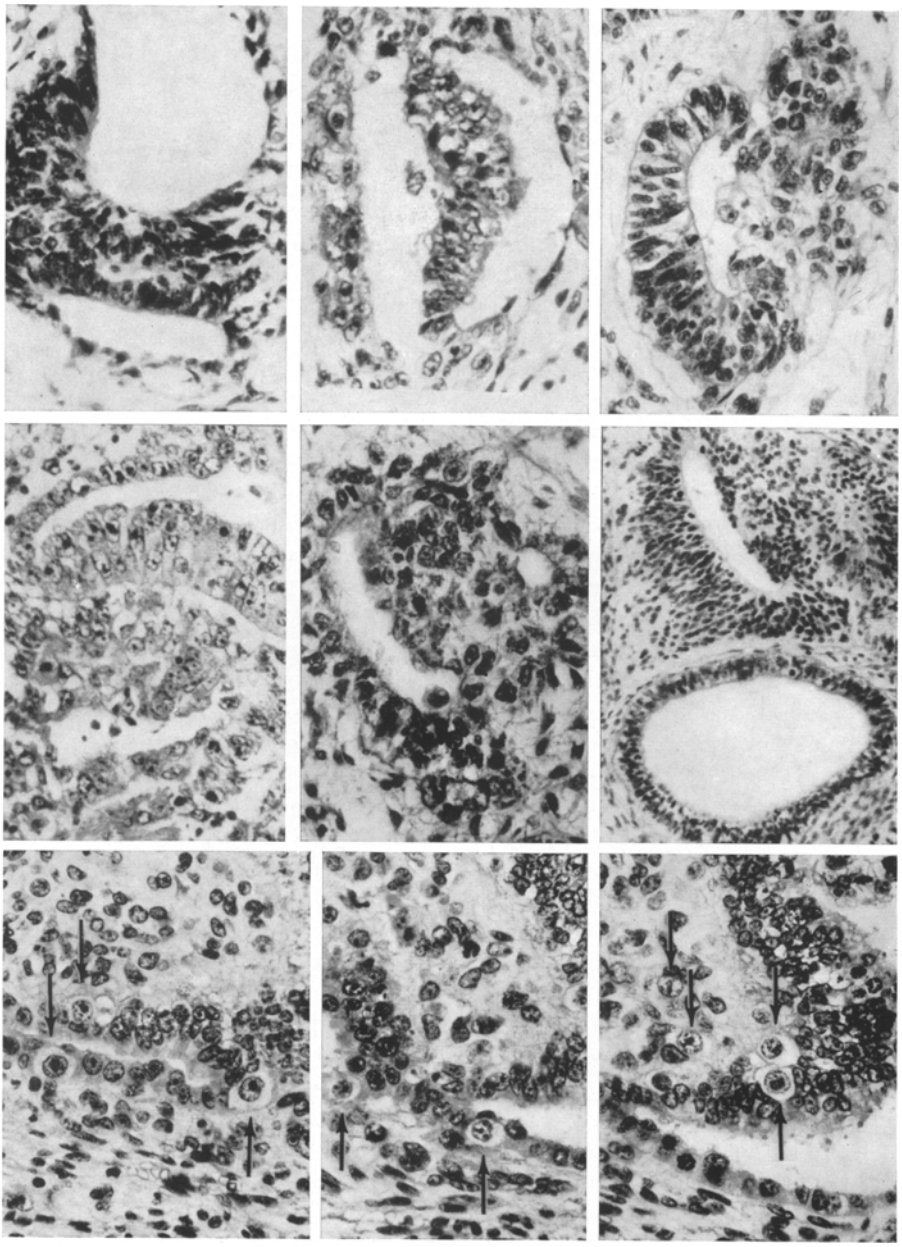
The embryoblastic stage of embryoid development (Figs. 10—15 and 19) includes all forms in which the embryoblast has developed and organized as an embryo. The embryoblastic components became the ectoderm with the amniotic cavity, the endoderm with the yolk sac cavity and the embryonic mesoderm. These structures have organized themselves to constitute small units which are similar to early stages of mammalian embryos. The embryoids of this group are generally surrounded by clear stroma similar to the stroma already encountered in earlier forms. This stroma surrounds completely the embryoid structure and it is composed of stellate clear cells in a watery matrix (Figs. 12—14).

The embryoids of this group show different degrees of development ranging from earlier forms composed of two embryonal germ layers to embryoids with three well-established layers. The youngest forms of this stage (Figs. 11—12) are composed of single embryonic discs without a distinct separation of the ectodermal and the endodermal cells. The intermediate stages (Figs. 10) show well formed embryonic discs with the ectoderm and the endoderm clearly distinct

Fig. 7. Blastocyst-like embryoid showing mitoses in the inner cell mass and central cavitation. From the testicular teratoma. ×275

Fig. 8. Blastocyst-like embryoid encountered in a large space showing some advanced development of its embryoblast. From the ovarian teratoma. ×275

Fig. 9. Blastocyst-like embryoid encountered in a vein showing mitosis and amniogenesis of its embryoblast. From the testicular teratoma. ×400



10—12

13—15

16—18

Fig. 10. Embryoid at an intermediate embryoblastic stage showing the amniotic cavity (above) the embryo proper (middle) and the yolk-sac cavity (below). The embryo shows clearly its ectoderm and endoderm. From the ovarian teratoma. ×250

Fig. 11. Embryoid at an early embryoblastic stage showing the amniotic cavity (left) the embryo proper (middle) and the yolk-sac cavity (right). The embryo is composed of a single embryonic disc. From the testicular teratoma. ×200

Fig. 12. Embryoid at an early embryoblastic stage showing a single embryonic disc. Notice the clear watery stroma which surrounds the embryoid. From the ovarian teratoma. ×200

Fig. 13. Embryoid at an advanced embryoblastic stage showing the amniotic cavity (above) the embryo proper (middle) and the yolk-endodermic cavity (below). The embryo proper is composed of ectoderm, mesoderm and endoderm. From the testicular teratoma. ×200

and absence of embryonic mesoderm. The more advanced stages (Fig. 13, 14) show clearly the ectoderm, endoderm and embryonic mesoderm. Some embryoids of this stage show a high degree of embryoid organization. Advanced embryoids show a well developed ectoderm with its amniotic cavity, a well developed embryonic mesoderm and an elongated endodermic tube showing a posterior prolongation which may represent an allantoic-like formation (Fig. 19).

The trophoblastic stage of embryoid development (Figs. 20—23) includes the most uncommon group of embryoids encountered in teratomas. They are characterized by the development and organization of both the embryoblastic and the trophoblastic elements. The distinct characteristic is their trophoblastic organization which ranges from amorphous masses composed of both the cyto- and syncytiotrophoblastic cells to highly organized previllous, lacunar placenta-like formations. The trophoblastic elements enclose, partially or completely, the embryo proper.

The most common forms encountered in this group are those with incompletely formed trophoblastic structures (Figs. 20—21). They are composed of an embryo proper at an embryoblastic stage of development partially enclosed by the developing trophoblastic cells. The trophoblastic cells are of two distinct types: the inner cells or cytotrophoblasts which are closer to the embryo proper and usually in contact with its amniotic cavity are characteristically large and clear. The outer cells or syncytiotrophoblasts are distant in location and composed of large masses of multinucleated cells with dark cytoplasm. The syncytiotrophoblasts are always established themselves in spaces, probably formed by their own action which are vascular sinusoids and contain blood (Figs. 20—23). The syncytiotrophoblasts show marked tendency to invade surrounding tissues in which they established the vascular sinusoids. The trophoblastic cells when encountered near to the embryoid have normal morphologic appearance. However, those masses of trophoblastic cells distant to the embryoids or those encountered without any apparent relation to them, show anaplasia.

The degree of placenta-like organization which some of these embryoids can achieve is remarkable. The embryoid structure of Fig. 22b and the accompanying ink-drawing copy of it (Fig. 22a) is an unique example. This embryoid is described in detail. It consists of a central embryonic cavity containing the embryo proper, surrounded by a placenta-like formation. The embryo proper shows signs of degeneration and the embryonic cavity is filled with fragmented and pyknotic cells. In spite of the degeneration of the embryo proper the ectodermal disc, the endoderm, and a few mesodermal cells can still be recognized. The embryonic cavity is enclosed by a continuous layer of trophoblastic cells. The trophoblastic cells of this embryoid can be separated in three groups, the inner, the intermediate and the outer. The inner and intermediate groups are composed of cytotrophoblasts and the outer by syncytiotrophoblasts. The inner group of

Fig. 14. Embryoid at an advanced embryoblastic stage showing the amniotic cavity (left), the embryo proper with mesodermal elements (middle) and a yolk-endodermic tube (right). This embryoid is surrounded by clear watery stroma. From the testicular teratoma. ×250

Fig. 15. Advanced development of an embryoid showing a developing neural tube (above) and an endodermic, mucus producing, epithelial cavity. From the ovarian teratoma. ×70

Figs. 16, 17, 18. Three near consecutive sections of the yolk-endodermic cavity of an imperfect embryoid showing (arrows) typical cells considered to be primordial germ cells. From the testicular teratoma. ×350

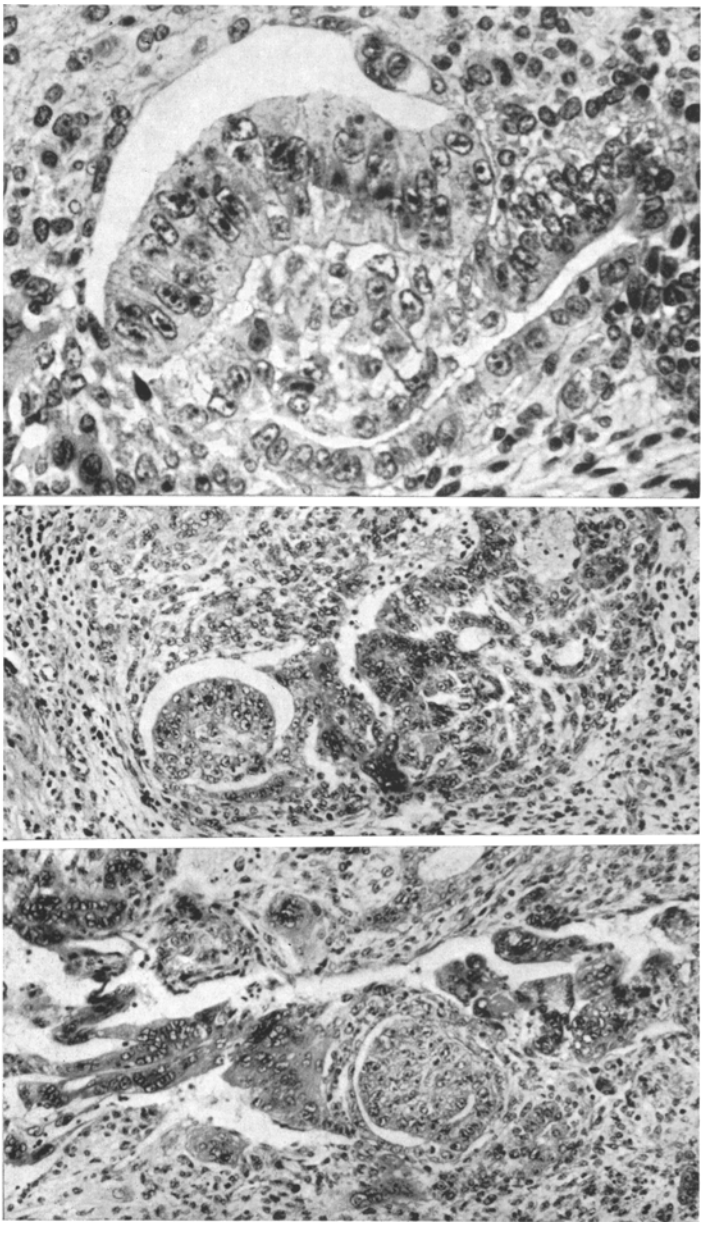


Fig. 19. This embryoid at an advanced embryblastic stage depicts a high degree of embryoid organization. The amniotic cavity (above), the ectodermal disc, the mesoderm (center) and the yolk-endodermic tube with a posterior allantoic-like structure. From the testicular teratoma. ×450

Figs. 20, 21. Two embryoids at a trophoblastic stage showing the embryos proper (arrows) at an embryoblastic stage and an amorphous placenta-like formation. The cytotrophoblast closer to the embryos and syncytiotrophoblast distant to the embryos and in vascular sinusoids are clearly recognized. From the testicular teratoma. ×175

cytotrophoblasts constitute a continuous layer of proliferating cells enclosing the embryonic cavity. The intermediate group of cytotrophoblasts which is a continuation of the cells of the inner group are arranged in a trabecular archi-

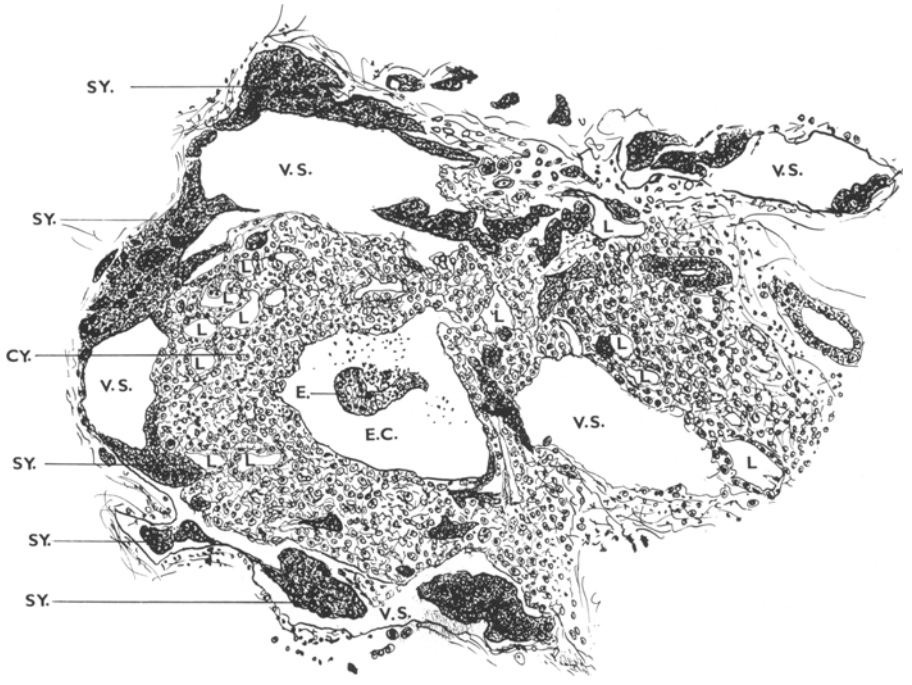


Fig. 22a. Ink drawing copy of an enlarged photograph of the embryoid depicted in Fig. 22. For identification of its components and better understanding of its nature. *SY.* Syncytiotrophoblast, *CY.* Cytotrophoblast, *V.S.* Vascular sinusoid, *L.* Lacuna, *E.* Embryo proper, *E.C.* Embryonic cavity

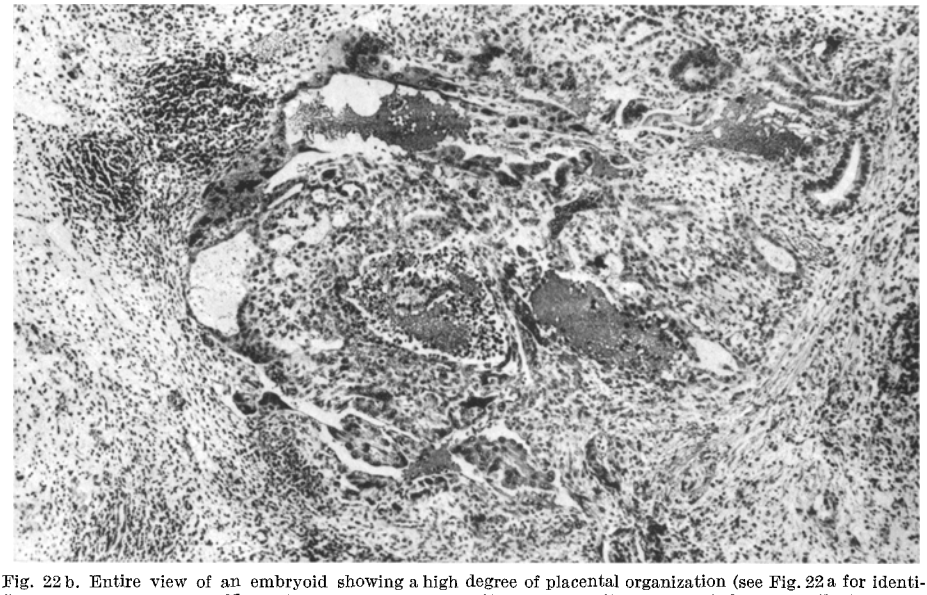


Fig. 22b. Entire view of an embryoid showing a high degree of placental organization (see Fig. 22a for identification of its component). Notice that the vascular sinusoids are filled with blood (not showing in the text-fig.). Primitive mesodermal stroma surrounded the embryoids. The lacunae are filled with serum. The availability of blood may explain the extraordinary organization achieved by this embryoid. From the testicular teratoma. ×50

tecture. Between the trabeculae, lacunar spaces are established which contain fluid with granular eosinophilic precipitate, probably serum. Some of the most

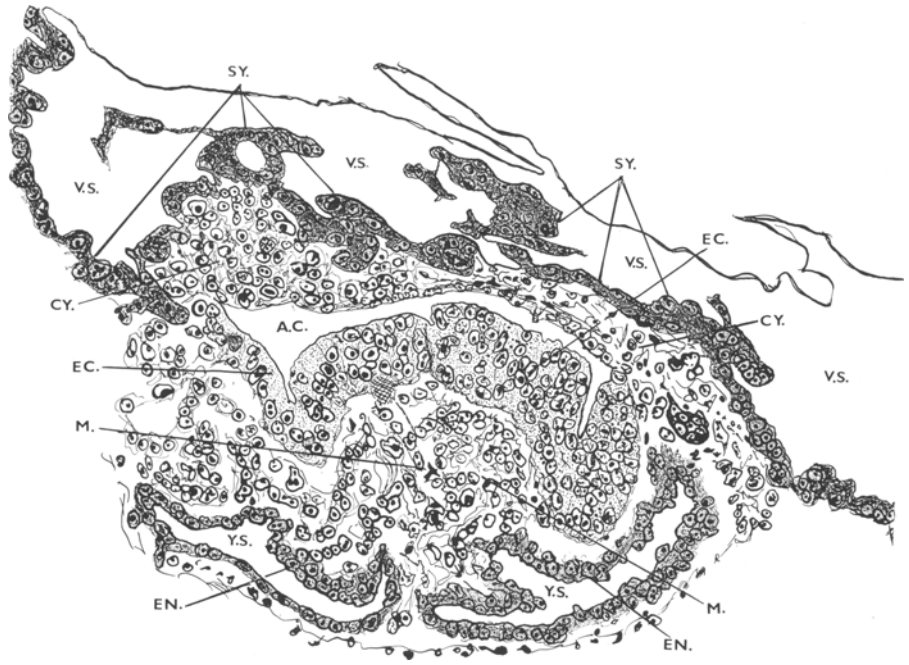


Fig. 23a. Ink drawing copy of an enlarged photograph of the embryoid depicted in Fig. 23. For identification of its components and better understanding of its nature. *A.C.* Amniotic acvity, *EC.* Ectoderm, *EN.* Endoderm, *M.* Mesoderm, *Y.S.* Yolk-sac

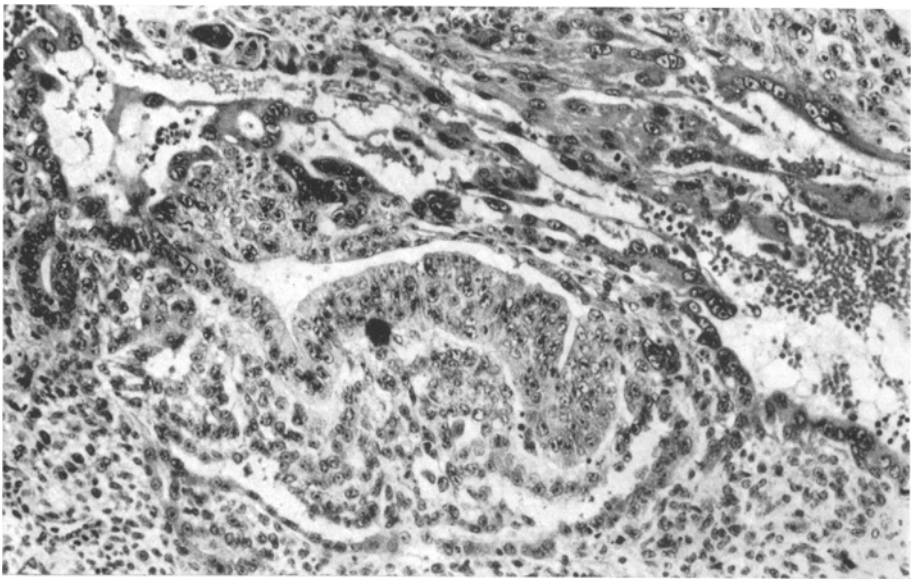


Fig. 23b. A monoamniotic, monochorionic conjoined twin embryoid (see Fig. 23a). The vascular sinusoid is filled with blood. The syncytiotrophoblasts are easily recognized by the dark cytoplasm and the formation of syncytical cellular masses. The cytotrophoblast appeared closed to the amniotic cavity. The double ectodermal structures and the yolk-endodermal cavities are easily recognized. From the testicular teratoma. ×220

peripheral lacunae open into large vascular sinusoids which contain blood. The trophoblast in contact or lying in the vascular sinusoids becomes the syncytio-

trophoblast. The syncytiotrophoblast are characterized by large cellular masses of multinucleated cells with dark cytoplasm. The lacunar stage of trophoblastic differentiation with vascular sinusoids of this embryoid corresponds almost exactly to the lacunar stage (11th or 12th day) of a previllous human placenta.

Another unique embryoid of this group to be described in detail is shown in Fig. 23b and the accompanying ink-drawing copy of it (Fig. 23a). This embryoid represents a form of twinning. It is composed of a single amniotic cavity, a conjoined double embryo and a partially established trophoblastic structure. The trophoblastic cells have developed from an area closer to the amniotic cavity and its cytotrophoblastic and syncytiotrophoblastic cells are easily recognized. The syncytiotrophoblast is growing in cellular masses into a large vascular sinusoid containing blood. The ectodermal disc is an elongated structure composed of two joined portions each having a deep depression, probably representing the primitive streak. The embryonic mesoderm appears to be shared by both structures since it does not show any distinct morphologic separation. The endodermal cells and the yolk sacs cavity are doubled, each corresponding to one of the conjoined embryos. This embryoid represents a monoamniotic and monochorionic conjoined twin.

Imperfect embryoids

In both of the teratomas studied many embryoid structures were encountered which did not show or have the necessary morphologic organization to be classified in any of the four stage just described. All these embryoids are separated into a group of incompletely or imperfectly formed embryoids. These embryoids include a great variety of forms of which the most easily recognized ones are the amnio-ectodermic, the yolk-entodermic and mixed ecto-endodermic vesicles at early developmental stages. The main characteristic of this group is their incompleteness. Morphologically they appeared as portions or fragments of complete embryoids. Embryonic and extra-embryonic mesoderms constitute the supporting stroma of these embryoids and occasionally they may be themselve the only component of an embryoid. These imperfect forms of embryoids may continue their embryonic development toward histologic maturity (Fig. 15). Intermediate stages of the histogenesis of many tissues were found in both teratomas. Examples of imperfect embryoids are encountered in the literature and there is not need in here to describe them in detail.

Amorphous embryoids

The last group of embryoid structures includes a rather heterogeneous group, characterized by actively proliferating embryonic tissues. The distinct morphologic characteristics of these embryoids are their lack of maturation, remaining as embryonic tissues, and their lack of embryoid organization. The following embryoid structures can be recognized in this group: Proliferating embryonic ectoderm, proliferating embryonic endoderm, proliferating embryonic mesoderm, proliferating extra-embryonic mesoderm, proliferating embryonic trophoblast and mixed forms. Rarely, any of these embryoids are composed by a single proliferating tissue, usually a mixture is encountered in which the components can be easily recognized. These proliferating embryonic tissues constitute the main substrate for the malignant portions of the teratomas.

Finally, in some complete embryoids at the embryoblastic stage and in portions of them (imperfect embryoids) a typical type of cells is encountered. These cells are large, round, with a clear cytoplasm, round nucleus with a distinct central nucleolus and a prominent nuclear membrane (Figs. 16—18). These cells are typically located in the endoderm of the embryoids (Figs. 16—17) and in other locations in which they appeared to accumulate (Fig. 18).

Some differences existed between the female and male tumors studied in reference to their embryoids. The complete forms of embryoids are common in both tumors. However, the embryoids of the trophoblastic stage were almost exclusively found in the male teratoma. Highly organized trophoblastic elements forming a placental structure were not seen in the female teratoma. The imperfect forms of embryoids were more common in the female teratoma. The amorphous forms of embryoids were more common in the male teratoma. The great variations of immature embryonic tissues was a characteristic of the male teratoma studied.

Discussion

A great variety of structures morphologically resembling early stages of the development of human embryos has been presented and described. These structures were encountered in only one ovarian and one testicular teratoma. These two teratomas were selected because both were composed of all the tissues which are characteristic of teratomas in general. All structures encountered in those two teratomas which resemble complete embryos or only portions of them, were named "embryoids" (embryo-like structure). All the embryoids were separated in three main categories: the complete, the imperfect and the amorphous forms. Each category includes several types of embryoids.

The existence of such embryoids in teratomas should be accepted not as a mere occurrence, but as a significant biological phenomenon of these tumors. With the exception of the amorphous embryoids which remain unchanged as primitive embryonic tissue, the embryoids show a tendency to mature histologically. Some embryoids evolve through a process of embryonic development which ranges from early forms of development to highly organized embryos and placental structures. The capacity of complete embryoids and of portions of them (imperfect forms) to evolve through an embryonic development and to mature histologically became their most important biological property. This property could explain by itself the basic architectural pattern and the evolution of human teratomas. The biological capacity of the embryoids to undergo embryonic development implies that a teratoma acquires its multiple tissues through the embryonic development and maturation of its embryoids. The embryoids encountered in teratomas are characterized by their multiplicity and by difference in their developmental ages which suggests that embryoids are being formed at different times during the evolution of the teratoma.

The fact that not all embryoids encountered in teratomas are completely formed suggests the existence of some factors which facilitates and allows the complete development of some of them. Two possible factors have been established on purely morphologic basis. The first consists in the formation of a watery and clear stroma around the embryoids. This stroma becomes a distinct characteristic of embryoids and appears to be induced by them. This stoma appeared also to

play a role in the nutrition, in the insulation and in the preservation of the developing embryoid. These protective mechanisms may permit the embryoids to develop independently from its surrounding and subsequently achieve greater organization. The second factor consists in the availability of blood to the developing embryoid. Advanced embryoid forms, especially at the trophoblastic stage are always surrounded by large sinusoidal spaces which are filled with blood. It appears that the development of these structures depends on the amount of blood available to them. It is possible that the lack of embryonic development beyond the embryoblastic and the trophoblastic stages (described above) may be explained by the lack of an appropriated nutrition for the entire embryo. This will explain the fact that only portions, those well nourished, of the embryoids are capable of complete embryonic maturity. These portions become the mature tissues of teratomas.

The imperfect or incomplete forms of embryoids share the same biological properties with the complete forms of embryoids. The cystic nature (vesicles) of these embryoids is significant since it could explain some morphologic aspects of the teratomas. There have not been good explanations for the cystic nature of the mature tissues encountered in teratomas. Of all cystic structures of a teratoma those lined by mature skin with its appendages are the hardest to interpret. The skin and its appendages should cover the outside rather than lining the inside which is a *sine qua non* in teratomas. The imperfect forms of embryoids are almost without exception constructed as small vesicles. The amnio-ectodermic, the yolk-entodermic or the mixed ecto-endodermic vesicles are the most commonly found. The development toward histologic maturity of this vesicle will necessarily result in cystic or tubular structures lined by mature tissues derived from the original components. A characteristic of this group of embryoids is their abundance which will explain also the multiplicity of mature cystic tissues encountered in teratomas.

The last category of embryoids described constitutes a heterogeneous group characterized by failure of histologic maturity beyond early stages of embryonic development, and by the lack of an embryoid organization. The embryoids of this group are formed by proliferating embryonic tissues representing the group of the so-called embryonal carcinomas of the testis and rarely of the ovaries. The application of the embryologic knowledge to the morphologic appearance to the different pattern presented by the embryonal carcinomas yields some meaning and significance to its tissue components. The classical solid pattern of embryonal carcinoma is actually a proliferating embryonic ectoderm. The adenocarcinoma or adenomatoid pattern represent a proliferating endoderm. The mesodermal or reticular pattern correspond to proliferation of embryonic mesoderm and probably of extra-embryonic mesoderm. Mixed patterns of embryonal carcinomas are composed of various of the tissues described above. The chorio-carcinomas are represent the proliferation of trophoblastic embryonic elements away from the embryoids. The justification for the formation of a group of amorphous embryoids is based in the need to establish the embryonic nature of the group of embryonal carcinomas. Also, to point upon the fact that the different pattern presented by these carcinomas are actually the result of the proliferation of identifiable embryonic tissues.

In teratomas the balance between the embryoids capable of histologic maturity with those which remain immature as embryonic tissues may be directly related to its benign or malignant behavior. Teratomas in which all of their embryoids have matured histologically behave as biologically benign (cystic) teratomas. This type of mature benign teratoma is very common and occurs frequently in the human ovary [WILLIS (2)], in the testis of horses (WILLIS and RUDDUCK) in experimentally induced testicular teratomas in the fowl (MICHALOWSKY; BAGG; GUTHRIE) and in some instances in testicular teratomas of man [WILLIS (1)] and mice (STEVENS and HUMMEL). Teratomas in which the majority of its embryoids failed to undergo histologic maturity remaining as embryonic tissues, behaved as malignant teratomas. The testicular teratomas in man are the classical example of this last group of immature teratomas. Intermediate forms between these two extremes are common in both female and male teratomas.

The origin of the embryoid structures within the teratomas becomes an obvious problem since only one type of cells is capable of embryonic development, namely the germ cells. Several stages are recognized in the maturation of germ cells, the primordial germ cell, the terminal haploid cells and, in between, several cellular stages during the process of meiosis. Of all these stages only the primordial or the pre-meiotic germ cell in both sexes is capable of embryonic development (parthenogenesis) by itself as well as the haploid ovum. A primordial germ cell can be compared biologically with an early blastomere which also is capable of embryonic development by itself. The primordial or premeiotic germ cells become segregated early in embryonic development (MCKAY, HERTIG, ADAMS and DANZIGER), migrate to and remain unchanged in the gonads (MCKAY, HERTIG, ADAMS and DANZIGER; WITCHI; MEYER) (and possibly in extra-gonadal middle line structures) until the process of meiosis begins. Until this time the primordial germ cell is probably capable of embryonic development by itself as are the early blastomeres. Parthenogenesis of primordial germ cells will result in the formation of pathologic embryoids. The possibility that the primordial germ cells are the origin of teratomas has been suggested and denied many times [DIXON and MOORE (1, 2); GAILLARD (1, 2); MASSON; NICOD; PEYRON (1); STEVENS; WILLIS (1)]. However, how the germ cell accomplishes the formation of teratomas remains an obscure problem and a matter of some speculations [GAILLARD (2); MASSON; PEYRON (1); STEVENS]. The findings and observations presented here suggest the following explanation.

Parthenogenesis of female or male primordial (pre-meiotic) germ cells may lead to the formation of parthenogenetic embryoids capable of undergoing embryonic development. The embryonic development of the embryoids can follow two directions. A development toward the histologic maturity of their components or a failure to do so in which case the embryoids components remain as proliferating primitive embryonic tissues. These two directions of growth can explain the general architecture of teratomas as well as their benign or malignant biological behavior respectively. Local environmental and nutritional factors and the actual nature of the primordial germ cell in itself are the fundaments on which the future evolution of the embryoids depend. The existence in embryoids of large cells morphologically identical to primordial germ cells described first by Peyron

[PEYRON (10—12)] and confirmed (Figs. 16—18) by the present study becomes a phenomenon of great significance. It supports the idea of the real embryoid nature of the structures and intriguing possibilities to be investigated are opened by their mere existence in embryoids. One of these possibilities will be the capacity of some embryoids to reproduce themself through parthenogenesis of its own primordial germ cells.

The study of the embryoid structures presented and discussed above is actually a study of the basic biology and nature of teratomas. The origin, the nature and the significance of the embryoid structures studies are actually the same thing as the origin, the nature and the significance of teratomas. *Each teratoma becomes the biological expression of its own embryoids originally derived from parthenogenesis of primordial germ cells.* Table 2 represents schematically the ideas expressed above.

Table 2. *Schematic representation of the suggested origin of teratomas (teratogenesis) based on evolution of its embryoids*

Teratogenesis: parthenogenesis of primordial germ cells with formation of embryoids			
Tendency to remain immature		Evolution of embryoids	Tendency to histologic maturity
Malignant behavior			*Benign behavior*
Carcinoma . . .	Proliferating ectoderm	Ectoderm	Ectodermal derived tissues
Adenocarcinoma	Proliferating endoderm	Endoderm	Endodermal derived tissues
Mesodermal . .	Proliferating mesoderm	Mesoderm	Mesodermal derived tissues
Reticular	Proliferating extra-embryonic mesoderm	Extra-embryonic mesoderm	Extra-Embryonic mesodermal derived tissues
Choriocarcinoma	Proliferating trophoblast	Trophoblast	Trophoblastic elements of the placenta of embryoids

The present study hopes to establish the embryoid nature of teratomas. It introduces a new approach to the study of the biology of teratomas and it hopes to stimulate future investigations in the fields of evolution and nature of human and experimental teratomas.

Summary

A study of the embryoids (embryo-like structures) encountered in one ovarian and one testicular teratoma is presented. Both teratomas are mixed types and composed of all types of tissues which are encountered in teratomas. The embryoids are classified according to their morphologic characteristic and their embryonic age. Three main categories of embryoids are recognized: the complete, the imperfect and the amorphous forms. Each category is composed of several types of embryoids. The advanced forms of the trophoblastic stage of embryoid development are presented and described for the first time. The embryoids are considered to be derived from parthenogenesis of primordial, premeiotic germ cells. The embryonic evolution of these embryoids constitutes the architecture of the teratomas. The benign or malignant behavior of a teratoma depends on the tendency toward histologic maturity or immaturity of its embryoids respectively.

Ursprung, Beschaffenheit und Bedeutung der „Embryoide" in menschlichen Teratomen

Zusammenfassung

Untersucht wurden die Embryoide (embryonenähnlichen Strukturen) in einem Teratom des Ovariums und einem des Hodens. Beide Teratome gehörten dem gemischten Typus an und waren aus allen Geweben zusammengesetzt, welche man in Teratomen antreffen kann. Die Embryoide wurden nach ihren morphologischen Kennzeichen und ihrem embryologischen Entwicklungsalter in drei Hauptgruppen eingeteilt: die vollständigen, unvollständigen und amorphen. Jede dieser Gruppen enthält wiederum mehrere Typen von Embryoiden. Die vorgeschrittenen Formen, die dem Trophoblastenstadium der Embryogenese entsprechen, werden hier zum ersten Mal genauer beschrieben. Es wird angenommen, daß die Embryoide zurückgehen auf die Parthenogenese von primordialen, prämeiotischen Keimzellen. Die Embryonalentwicklung dieser Embryoide liegt der Architektur der Teratome zugrunde. Das gut- oder bösartige Verhalten eines Teratoms hängt von der Neigung seiner Embryoide zu histologischer Ausreifung oder Unreife ab.

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