

The Relationship of Twins, Teratomas, and Ovarian Dermoids

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INTRODUCTION

The bizarre structure of teratomatous tumors has long excited interest. Unlike other neoplasms, the teratomas are composed, characteristically, of more than a single type of cell and are related, histogenetically, to more than one of the three embryonic germ layers. The constituent elements of these tumors may be quite foreign to their site of origin in the body and, in their arrangement, tend to mimic organs or even organ systems. The abortive or imperfect character of this resemblance finds reflection in the name, first applied by Virchow (15), of "teratoma," a malformed or "monstrous" tumor.

It is natural that the morphologic peculiarities of the teratomas should have led to the formation of theories of pathogenesis differing from those associated with other tumors. With its pleomorphic, organoid character, a teratoma represents in itself, as expressed by MacCallum (9), "a frustrated attempt at the formation of a human body in which the whole plan has failed through the lack of the necessary parts, and the distortion and disarrangement of those which were available."

Two alternative mechanisms might reasonably explain the occurrence of such an ontogenic fiasco. First, there is abortive parthenogenesis. Second, there is inclusion of isolated blastomeres.

A teratoma might be the end result of spontaneous development of unfertilized germ cells, ova or sperm. Several facts are in favor of such a view. The gonads are among the commoner sites occupied by tumors of this group. Dermoids comprise approximately 18 per cent of proliferative ovarian neoplasms (14), while tumors of the testis are quite commonly teratomatous. Michalowsky (11) and Bagg (1) have produced teratomas of the testes in the rooster, by the injection of zinc chloride solutions. Bosaeus (2) demonstrated the production of teratomas in frogs by the reimplantation into the mother's body of eggs that had been removed and mechanically stimulated to develop parthenogenetically. Earlier, Loeb (7) described the occurrence of teratoid structures in the ovaries of virgin guinea pigs, and pointed out their importance

as putative links between unfertilized ova and true teratomas, evolved through parthenogenesis.

A teratoma might also be formed by the isolation and inclusion of a blastomere in the body of the embryo that develops into the host of the teratoma. Segregation of such a relatively undifferentiated cell, or group of cells, with temporary inhibition of its development, might result in the formation of a "cell rest," in the sense of Cohnheim (3) and Ribbert (12), that would have sufficient multipotency to produce a teratoma, once it became reactivated. This theory, too, gains support from diverse facts. As emphasized by Marchand (10), Schwalbe (13), Greil (5), and others, it is possible to construct complete morphologic series of cases ranging from equal conjoined twins through irregular parasitic conjoined twins, and through the more complex embryomas to the characteristic teratomas. So many intergrades exist, anatomically, between twins and teratomas, that one might naturally expect to find common, or at least similar, modes of production of twins and teratomas. While knowledge of the actual mechanism of human twinning is still inferential, it seems most likely that the process involves a splitting of the zygote with developmental separation of component portions. Whether "identical" or "fraternal" twins are produced by similar or by dissimilar mechanisms is an important, but unsettled question. Curtius and von Verschuer (4) believe the mechanisms are similar; most other authors believe them dissimilar. At least one type of twin, however, is formed by a process so closely analogous to that postulated by the inclusion theory of teratoma formation, that such variables as time of fission or relative proportions of the divided segments offer themselves as logical modifiers determining whether twin or teratoma is the end result.

The teratomas encountered in extragonadal locations are most frequently situated in or near the midline of the host. The sacrococcygeal region is a classic site. It seems hardly coincidental that the midline is a common axis of symmetry in cosmobia (equal and unequal) or that the sacrococcygeal region is an equally classic site of fusion of conjoined twins.

The occurrence of teratomas in infants at an age when developmental inclusions would seem more plausible than abortive parthenogenesis, is a final point in favor of the inclusion theory.

There remains a third possibility. There may be, as suggested by MacCallum (9), more than one type of teratoma, referable to more than one mechanism of production. Perhaps ovarian dermoids are produced parthenogenically while sacrococcygeal teratomas are the result of blastomeric segregation and inclusion.

If a relationship between twins and teratomas is possible, it would seem reasonable to enquire into the twin-like character of teratomas. The influence of heredity in twinning seems established by several statistical studies included in the literature reviewed by Greulich (6), although the mechanisms involved are uncertain. Is heredity, then, a factor in the production of teratomas? Reports of familial teratomas are rare (8). If, however, twins and teratomas depend on similar developmental mechanisms, may not a common factor of heredity be involved? If so, twinning would be associated with teratoma formation in families; twins would occur in the families of patients with teratomas more frequently than in a nontwinning or random population.

MATERIALS AND METHODS

With the above considerations in mind, patients with two types of teratomatous tumors and appropriate control patients have been investigated with respect to the occurrence of twins in their families. The tumor types selected were ovarian dermoids, and teratomas occurring in childhood.

The term "ovarian dermoid," as used in this study, refers to a cystic tumor of the ovary which, on pathologic examination, was found to contain hair and sebaceous material, frequently associated with additional structures such as teeth, cartilage, or glandular tissue.

The term "teratoma," as used in this study, refers to a cystic or solid tumor which, on pathologic examination, was found to contain more than one tissue element—nerve and muscle, hair and cartilage, etc. Eighteen of the teratomas included in the present study were situated along the spinal axis, while the following localities were involved in a single case each: mediastinum, retroperitoneal space, abdominal wall, pleural cavity, nose, and eyelid.

One of us (H.W.E.) has collected a series of 50 patients with ovarian dermoids, a series of 50 patients hospitalized for twin pregnancy, and a series of 40 patients hospitalized for singleton pregnancy. Each series was consecutive. In each case investigated, a pedigree was obtained from the propositus at a single interview in the hospital. The patients comprising

the first series were located through the pathologic laboratories of the Barnes, Maternity, and Jewish hospitals of St. Louis, of the Lying-In, City, Massachusetts General, and Peter Bent Brigham hospitals of Boston, and of the Free Hospital for Women in Brookline, Massachusetts. The patients of the second series were obtained similarly from the Maternity and the DePaul hospitals of St. Louis, and from the Lying-In Hospital of Boston. The entire third series was obtained from the last named institution. The authors offer their sincere thanks to the respective pathologists of these hospitals for their kind permission to carry on this study, and to their residents and secretaries for their invaluable assistance in securing interviews with the patients. Data were collected during the years 1935 through 1941, inclusive.

One of us (J.W.H.) has collected a series of 24 child patients with teratoma, a control series of 26 children having similar socio-economic status, and a control series of 24 students in the Harvard School of Public Health. In the first two series, pedigrees were obtained by interviews, sometimes repeated, with the parents and grandparents of the propositi in their homes. In the third series, pedigrees were obtained by questionnaires, filled in by the propositi. The cases of the first series form part of the collection of tumors of early life now under study in the Department of Pathology of the Children's Hospital of Boston. Data in this part of the study were collected in the years 1939 through 1941, inclusive.

The incidence of twins in these families was determined by two methods. The simplest method was based on the presence or absence of twins in each family, the family including, in this instance, blood relatives. The results are expressed in terms of the percentage of families with twins. The more detailed method of analysis consisted of determining the total number of twin births, the total number of single births, and of expressing the results in terms of the rate of twin births per thousand total births.

OVARIAN DERMIDS

The significant data obtained from the first three series are presented in Tables I and II. The first tabulation indicates the presence or absence of twinning in the entire family of the propositus, while the second records the rate of twinning in the sibship of the propositus. It is evident that occurrence of twins in the family is more common with patients with ovarian dermoids and with patients with twin pregnancy than with the random sample of population represented by the patients with singleton pregnancy. Both dermoid and twin series diverge from the singleton series by differences of similar magnitude. While these differences fail to exceed twice their

standard errors, owing to the smallness of the populations employed, they are probably real, because they correspond to differences obtaining in another type of analysis, twin birthrate method. The differences between the dermoid and twin series on the one hand, and the singleton series on the other, in regard to rate of twin births (Table II), are striking. That the respective differences between the series, analyzed by these two separate methods, should so agree is a fact that adds to the significance of the figure.

TERATOMAS IN CHILDREN

The significant data obtained from the second three series are represented in Tables III and IV.

TABLE I: INCIDENCE OF FAMILIES * WITH TWINS IN OVARIAN DERMOID SERIES AND IN CONTROL SERIES

Series	No. of families studied	No. of families including twins
Dermoid	50	28 (56%)
Twin pregnancy	50	†30 (60%)
Singleton pregnancy	40	16 (40%)

* "Family" as used in this table and accompanying discussion refers to the entire collection of blood relations included in the pedigree.

† Obviously every family in the twin series included one set of twins, the twin birth for which attention was drawn to the propositus. Only families with additional sets of twins, other than the initial set, have been credited in this table.

TABLE II: TWIN BIRTHRATES IN SIBSHIP OF PROPOSITUS IN OVARIAN DERMOID SERIES AND IN CONTROL SERIES

Series	Rate per 1,000 births
Dermoid	22.0
Twin pregnancy	18.0
Singleton pregnancy	5.3

In these tabulations, the two control series (families of children having socio-economic status similar to that of the children with teratomas, and families of students in the Harvard School of Public Health) were similar and therefore have been pooled. It is evident that the families of teratomatous children include twins more frequently than do the families of the individuals of the random control series. Further, the rate of twin births is higher in the former series than in the latter. Again, the similar divergences between the two series, in regard to the separate considerations of presence of twinning in the families and of twinning rate, mutually strengthen their significance. With the more extended pedigree information obtained in this part of our study, twin birthrates for the sibships of the parents of the propositi are available. As recorded in Table IV, there are equally impressive differences in rates between the tumor series and the control series.

DISCUSSION

Twin birthrates in the ovarian dermoid series, in the childhood teratoma series, and in the several control series may be compared with the twin birthrate reported by the United States Census. This later rate, 11.5 per thousand (a value exceptionally stable, since derived from a population representing a statistical "universe") is very similar to the rate for the control series of mothers hospitalized for singleton pregnancy, and the rate for control nontumorous children and students of the Harvard School of Public Health, indicating adequate control. The twin birthrates obtained for the twin pregnancy series, for the ovarian dermoid series, and for the childhood teratoma series are all similar and are all much in excess of the controls.

TABLE III: INCIDENCE OF FAMILIES WITH TWINS IN TERATOMA SERIES AND IN POOLED CONTROL SERIES

Series	No. of families studied	No. of families including twins
Teratoma	23	19 (83%)
Control *	50	17 (34%)

* The mode of selection of the control group is detailed in the text.

TABLE IV: TWIN BIRTHRATES IN THE FAMILIES OF THE TERATOMA SERIES AND IN POOLED CONTROL SERIES

Series	Rate per 1,000 births	
	Sibship of propositus	Sibships of parents
Teratoma	21	18
Control *	12	11

* See note, Table III.

Our cumulative data indicate a high incidence and rate of twinning in the families of patients with ovarian dermoids and in the families of patients with childhood teratomas, similar to the high incidence and rate of twinning in the families of mothers giving birth to twins.

This evidence is consonant with the idea that factors of heredity similar to those conditioning twinning may also condition the occurrence of ovarian dermoids and of teratomas of children. It favors the idea that ovarian dermoids and the teratomas of children are at least partly alike in mode of formation. Finally, a certain amount of support is given to the inclusion theory of the pathogenesis of the teratomatous tumors.

CONCLUSION

The incidence of twinning, whether measured by the percentage of families with twins or by the ratio of twin births to total births, is similar and con-

sistently high in families of patients with ovarian dermoids, of patients with childhood teratomas, and of patients with twin pregnancy—higher in each instance than in random control groups. This evidence supports a theory of similarity in pathogenesis of teratomatous tumors and of twins, probably involving common factors of heredity.

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