The origin of ovarian teratomas

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SUMMARY Chromosome and enzyme markers have been studied in 21 benign ovarian teratomas from 14 patients. Markers heterozygous in the patient were completely homozygous in 52% of the teratomas and completely heterozygous in 19%. The remainder showed a mixture of the two, 10%, having homozygous centromeres with some heterozygous enzyme markers and 19% having heterozygous centromeres and some homozygous enzyme markers.

These results suggest that benign ovarian teratomas in the present series arise from germ cells in a number of different ways. Those with heterozygous centromeres probably arise by failure of meiosis I. Some tumours with homozygous centromeres must arise by failure of meiosis II, but because of the low level of heterozygous enzyme markers in this group a substantial number are thought to arise by duplication of a mature ovum to give an entirely homozygous genotype, genetically the female equivalent of the complete hydatidiform mole.

Benign ovarian teratomas (dermoid cysts) are common tumours accounting for 10 to 20% of all ovarian cysts. They are formed of fully differentiated mature tissues, often from all three cell layers, and usually comprise a cyst containing sebaceous material, hair, and often teeth.1 Most of them have a normal 46,XX karyotype2 but mosaicism has been found in some.3

Early studies showed that tissue extracts and cultured cells from teratomas were frequently homozygous for enzyme markers which were heterozygous in host cells.4 5 Moreover, all centromeric chromosome markers heterozygous in the host were subsequently shown to be homozygous in the teratomas.6 7 This led to the conclusion that these tumours arose from a single germ cell after the first meiotic division. Studies in a strain of mice where a high proportion develop spontaneous ovarian teratomas indicate that these may arise in essentially the same way.8

If this interpretation is correct, analysis of genetic markers in teratomas should provide a means of estimating the genetic distance between any given locus and the centromere, since heterozygosity could only arise as a result of recombination. Of course, only teratomas occurring in subjects who happen to be heterozygous for the locus in question would be informative. Assuming that all teratomas arise in the same way, Patil and co-workers9 calculated the gene-to-centromere distances of phosphoglucomutase 1 (PGM1), phosphoglucomutase 3 (PGM3), and phosphogluconate dehydrogenase (PGD) as 20, 17, and 33 centimorgans (cM), respectively. These figures contrast with estimates of 68, 4, and 133 respectively which have been obtained in females from family studies9 (table 1). From our own data, we have previously observed that for loci known to lie far from the centromere very few tumours are heterozygous, leading to estimates of gene-to-centromere distance much lower than expected.10 We suggested that suppression of crossing over might occur in these tumours. However, an alternative explanation would be that some ovarian teratomas arise by another mechanism.

We have explored this possibility by detailed investigation of ovarian teratomas in 14 patients. In each case karyotype analysis was performed on lymphocytes, on cells cultured from the teratoma, and where possible on cells cultured from normal solid tissue. Enzyme analysis was carried out on these cultures and also directly on the teratoma, on normal solid tissue, and on blood.

Materials and methods

Patients

Samples were obtained from 14 patients operated on at the National Temperance Hospital between December 1974 and August 1979. The patients were unselected; all those in whom adequate samples and...
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Table 1. Number of heterozygotes observed/total informative cases for 13 enzyme loci in 21 teratomas where the centromere status is known compared with number of heterozygotes predicted from family data.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Locus</th>
<th>Chromosome arm</th>
<th>Distance from centromere (Fc M)</th>
<th>Heterozygous centromeres (presumed failure of meiosis I)</th>
<th>Homozygous centromeres (presumed failure of meiosis II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>Phosphogluconate dehydrogenase</td>
<td>PGD</td>
<td>1p</td>
<td>133</td>
<td>3/4</td>
<td>2.64</td>
</tr>
<tr>
<td>α-fucosidase</td>
<td>α-FUC</td>
<td>1p</td>
<td>103</td>
<td>1/1</td>
<td>0.68</td>
</tr>
<tr>
<td>Phosphoglucomutase 1</td>
<td>PGM1</td>
<td>1p</td>
<td>68</td>
<td>6/7</td>
<td>4.90</td>
</tr>
<tr>
<td>Peptidase C</td>
<td>PEPC</td>
<td>2p</td>
<td>65</td>
<td>1/2</td>
<td>1.32</td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>ACPI</td>
<td></td>
<td>120</td>
<td>1/1</td>
<td>0.75</td>
</tr>
<tr>
<td>Glyoxalase I</td>
<td>GLO</td>
<td>6p</td>
<td>40</td>
<td>1/1</td>
<td>0.99</td>
</tr>
<tr>
<td>Phosphoglucomutase 3</td>
<td>PGM3</td>
<td>6q</td>
<td>4</td>
<td>1/1</td>
<td>0.99</td>
</tr>
<tr>
<td>Adenylate kinase 1</td>
<td>AKl</td>
<td>9q</td>
<td>130</td>
<td>1/1</td>
<td>0.99</td>
</tr>
<tr>
<td>Phosphoglycolate phosphatase</td>
<td>PGP</td>
<td>16q</td>
<td>60</td>
<td>1/1</td>
<td>0.78</td>
</tr>
<tr>
<td>Glutamate oxaloacetate transaminase (mitochondrial)</td>
<td>GOT2</td>
<td>16q</td>
<td>34</td>
<td>1/1</td>
<td>0.78</td>
</tr>
<tr>
<td>α-glucosidase</td>
<td>α-GLU</td>
<td>17q</td>
<td>74</td>
<td>1/2</td>
<td>1.36</td>
</tr>
<tr>
<td>Adenosine deaminase</td>
<td>ADA</td>
<td>20q</td>
<td>90</td>
<td>1/1</td>
<td>0.65</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>16/20</td>
<td>14.09</td>
</tr>
<tr>
<td>Malic enzyme (mitochondrial)</td>
<td>ME2</td>
<td>?</td>
<td>?</td>
<td>2/4</td>
<td>?</td>
</tr>
</tbody>
</table>

*Predicted values calculated according to Sturt, using the map distances shown in column 4 and assuming at least one cross over per chromosome arm, no interference across the centromere, and random segregation of chromatids in meiosis II (fig 5, 1b).

Successful cultures were obtained are included. Ten patients had single cysts (five on the right, three on the left, two side not known) and four patients had bilateral cysts, three having one in each ovary and one patient (DC 131) having six tumours on the right and two on the left. All tumours contained hair and sebaceous material and in most cases a copy of the histological report on the tumours was available, invariably confirming a diagnosis of benign ovarian teratoma. In two cases of multiple cysts (DC 86 and DC 131) one of the tumours was so small it was not sampled for fear of interfering with the histological diagnosis. The age of the patients ranged from 20 to 49 years and in most cases the teratoma was an incidental finding, frequently during pregnancy. None of the patients was known to have taken any fertility drugs. One patient with bilateral cysts (DC 118, aged 30) ascertained during pregnancy subsequently produced a child with trisomy 21.

Material was collected directly from the operating theatre and always dissected by the same person (SP). A piece from the centre of the dermoid cyst was removed, taking care not to include any material from the ovarian capsule. The part used for culture was always taken from the growth nidus and nearly always contained active hair follicles. A specimen of normal tissue was also collected, either from the ovary or Fallopian tube or, if this was not available, from the outer part of the cyst capsule. (Our previous studies had shown that this is always genetically representative of the patient rather than the cyst.) Small samples for culture were placed immediately in medium, the rest of the sample being stored at −20°C before enzyme analysis. The remainder of the specimen was sent for histology. Some days later the patient was visited on the ward and in all cases agreed to provide a blood sample after the project had been explained to her.

Methods

Cell culture

Small explants of the dermoid centre and of normal tissue were placed in Leighton tubes, immobilised with coverslips, and grown in Eagle’s MEM supplemented with 20% human serum or 10% fetal bovine serum (Flow Laboratories). One fibroblast growth was well established, all cultures were maintained in Eagle’s MEM containing 10% fetal bovine serum, Hepes buffer (10 mmol/l) (Hopkins and Williams), penicillin (100 IU/ml), and streptomycin (100 μg/ml).

Chromosome preparation and banding

Chromosome preparations were normally made between the third and seventh passage in culture. Metaphases were collected for 1 to 4 hours with colchicine, treated with hypotonic (0.075 mol/l KC1), fixed in acetate methanol, spread on cold slides, and air dried. Blood cultures were processed at 72 hours in the same way.

For Q banding, slides were stained in 0.5% atebrin (Gurr) in distilled water for 7 to 15 minutes, washed in tap water for 2 minutes, mounted in a thin layer of 12% sucrose solution, and viewed with a Zeiss fluorescence microscope. Q band heteromorphs were typed from photographs. At least three and up to 10 metaphases were examined for each tissue and classified according to the intensity of fluorescence (fig 1).
A modification of the method of Sumner\textsuperscript{13} was used for C banding. Slides were placed in 0.2 mol/l HCl for one hour, rinsed in deionised water, and treated with 5% barium hydroxide at 50°C for 15 seconds to 2 minutes depending on the age of the slide. They were then rinsed in deionised water, placed in 2× SSC at 60°C for one hour, and stained with 10% Giemsa (BDH) at pH 6.8. C bands were typed in at least 10 cells, both down the microscope and from photographs. They were classified according to relative size and position in relation to the centromere (fig 2).

**Enzyme analysis**
Tissues to be investigated directly were homogenised in a Silverson emulsifier with an equal volume of distilled water. After centrifugation at 10 000 g for 10 minutes, the supernatant was used for enzyme analysis. Red cell haemolsates were prepared by freezing and thawing packed washed red cells, and extracts of leucocytes and cultured cells were prepared as previously described.\textsuperscript{14, 15}

Enzyme analysis was done mainly by horizontal starch gel electrophoresis.\textsuperscript{16, 17} The typing of α-fucosidase and the subtyping of phosphoglucomutase (PGM1) were done by isoelectric focusing.\textsuperscript{18, 19}

A list of the polymorphic enzyme loci studied, together with what is known of their chromosome assignment and distance from the centromere, is shown in table 1. The chromosomal assignment is taken from a recent Human Gene Mapping workshop.\textsuperscript{20} Map distances have been estimated from family studies and are in female centimorgans. Many of the data are from Cook and co-workers,\textsuperscript{9} female distances being obtained by doubling male distances where no direct information was available, as suggested by these authors. More recent information was used for chromosome 1 and chromosome 16.\textsuperscript{22} As the number of polymorphic markers available increased during the span of this work, not every sample was tested for every enzyme.

**Results**

**CELL GROWTH**
Good growth was obtained from most of the cyst material. The resulting fibroblast cultures had the general appearance and growth pattern of those set up in our laboratory from skin biopsies. In contrast, good cultures from normal tissue were the exception. Growth after subculturing was always slow and it was often difficult to obtain enough cells for chromosome and enzyme studies. Host typing was therefore done mostly on blood, but where fibroblast cultures were obtained they were used as confirmation.

**KARYOTYPE**
Nearly all teratomas had a normal female karyotype although a few abnormal cells were found in some
### Table 2: Chromosome and enzyme markers in host and teratoma: patients with single cysts.

<table>
<thead>
<tr>
<th>Chromosome markers</th>
<th>Enzyme markers*</th>
<th>Zygosity of teratoma markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α-FUC</td>
<td>PGMI</td>
</tr>
<tr>
<td>1p</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1q</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2p</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6p</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6q</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>?</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>18/6</td>
<td>22/8</td>
</tr>
</tbody>
</table>

*For full names of enzymes see Table 1.

p, q, and s = short arm, long arm, and satellite of chromosome, respectively.

Q banding: b' = brilliant, b = bright, N = normal.

C banding: L = large, M = medium, S = small, pi = partial inversion, n = normal position, --- = not tested.
cultures. These are not thought to be relevant to the present discussion but will be the subject of a further communication.

**CHROMOSOME HETEROMORPHISMS**

Clear cut differences between the centromeric regions of at least two pairs of chromosomes were identified in normal tissue from each patient. Where results were obtained from both blood and fibroblasts derived from normal host tissue they were always in agreement. Chromosomes were studied in a total of 21 teratomas (tables 2 and 3). In any one tumour the centromere markers were either all heterozygous, as in the host (eight cases), or all homozygous (13 cases). However, both types of cyst could occur in the same patient. Examples of both homozygous and heterozygous teratomas are shown in figs 1 and 2.

**ENZYME RESULTS**

The results of testing the phenotype of the patient were consistent in blood and in other normal tissues tested, whether these were examined in fresh preparations or in culture. Some difficulty was experienced in assessing PGM3 and ACPI in fresh teratoma tissue. With the exception of DC 119 R cyst, which failed to grow in culture but produced very clear results from the tumour extract, all the enzyme results on teratomas described here were confirmed in cell cultures.

Tables 2 and 3 show the enzyme results for all enzyme loci where the patient was heterozygous. In every case where the patient was homozygous the cyst was also homozygous, and these uninformative data are not shown. Examples of different enzyme phenotypes in multiple tumours from two different patients are shown in figs 3 and 4.

In most of the teratomas the enzyme markers were either all homozygous or all heterozygous, resembling

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**FIG 3** PGD isozymes in cells cultured from seven separate teratomas occurring in DC 131.
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The results found for centromeric heteromorphisms. Four cysts were completely heterozygous for the enzyme and chromosome markers tested and thus were indistinguishable from host tissue. Four cysts in the multiple group, while heterozygous at the centromere, were homozygous for one or more informative enzyme markers. Only two cysts with homozygous centromeres, one in the single and one in the multiple group, were found to have both heterozygous and homozygous enzyme markers. Thus, taking all the teratomas together, 33% of the informative enzyme markers were heterozygous, but if we consider only the data from cysts with homozygous centromeres, the figure is much lower (7%) (table 4).

In summary, therefore, in this small series of 21 teratomas, 52% were completely homozygous, 19% completely heterozygous, 19% had heterozygous centromeres with some homozygosity of enzyme markers, and 10% had homozygous centromeres with some heterozygous enzyme markers.

Discussion

Chromosome and enzyme data from ovarian teratomas in the present series have in most cases shown clear cut differences between 'host' and teratoma, supporting previous conclusions that these tumours are of germ cell origin. In the four cases where such differences were not found, origin from somatic cells or, as in the earliest theories, from a blastomere which was an identical twin of the patient cannot be formally excluded. From the growth pattern of the cultures we feel fairly confident that the cells were indeed from the teratoma and not from contaminating host tissue.

The teratomas studied here differ substantially from those reported previously in that they show evidence of heterogeneous origin. In considering the possible ways in which these tumours might arise it is perhaps helpful to summarise the features of normal female meiosis, which involves two successive cell divisions referred to as meiosis I and II. Meiosis I is initiated in fetal life. Homologous chromosomes of primary oocytes pair and exchange genetic material during the pachytene stage of prophase. Chromosomes remain as bivalents (dictyotene) throughout childhood and only progress to metaphase I and cytokinesis in the adult ovary. Homologous chromosomes then separate into daughter cells, one of which is eliminated as the first polar body. The chromosomes proceed directly into metaphase II without DNA synthesis and at this stage ovulation occurs. The second maturation division (meiosis II) is normally only completed if fertilisation occurs and takes place in the tube rather than the ovary. It involves separation of the two sister chromatids to give two haploid daughter cells, one of which is eliminated as the second polar body. It appears that in the formation of ovarian teratomas, cells attempt to undergo, and sometimes complete, both divisions within the ovary. Abnormalities at various points in this process could result in cells from which a diploid tumour might arise. We can consider them in developmental sequence in relation to our own data.

### Table 4. Enzyme markers in 21 teratomas arising in 13 patients.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of cysts</th>
<th>Enzyme markers in cysts</th>
<th>Homozygous</th>
<th>Heterozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous centromeres</td>
<td>8</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Single cyst</td>
<td>5</td>
<td>17</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multiple cysts</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Heterozygous centromeres</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Single cyst</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>45</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Failure of meiosis I (fig 5.1)

Tumours arising by this mechanism would be heterozygous for chromosome and enzyme markers near the centromere. Some homozygosity at more distal loci would be expected to arise as a result of crossing over and segregation of homologous loci. All eight tumours heterozygous at the centromeres could have arisen in this way. The number of

![Fig 4. Acid a-glucosidase isozymes in a placental control and in cultured cells showing different homozygous phenotypes in the two cysts of DC 118. Chromosome analysis on these cysts (fig 1) showed one to have heterozygous centromeres.](image-url)
heterozygous enzyme loci in these tumours is shown in table I and agrees closely with expected values.

**Failure of Meiosis II (Fig 5 II)**

Tumours arising by this mechanism would be homozygous for centromere markers and for those loci very close to the centromere. Loci more distal from the centromere would be expected to be heterozygous in some cases as a result of crossing over. This is the mode of origin which has been suggested previously for ovarian teratomas, and each of the 13 tumours homozygous at the centromere in our own series could have arisen in this way. There is, however, a difficulty when all 13 tumours

![Diagram of meiosis I and II](http://jmg.bmj.com/1984/0020-5359-00001366/fig5.jpg)

**Fig 5** Possible mechanisms of origin of ovarian teratomas. I. Suppression of meiosis I. II. Suppression of meiosis II. III. Normal meiosis followed by duplication of haploid gamete. Each horizontal line represents a chromatid. a and b refer to non-cross over and cross over respectively. A and C represent alleles for an enzyme marker some distance from the centromere which could be distal to a cross over. M and S refer to medium and small C band centromere markers respectively. The consequences of each mechanism for the teratoma are as follows: IIIa, IIIb, and Ila. Both centromere and enzyme markers have to be homozygous. IIIb. Centromeres homozygous, enzyme marker heterozygous. Ia. Both centromere and enzyme marker heterozygous. Ib. Centromeres always heterozygous, enzyme markers can be either homozygous or heterozygous. *Chromosomes enclosed within an ellipse denote those going into a polar body. There is an equal chance that either product of division will enter the polar body. Not all the possible combinations are illustrated.
are considered together, because the proportion of markers in these tumours which are heterozygous even at distal loci is extremely low (7%).

Several authors have suggested functions which would relate heterozygosity (equivalent to second division segregation in normal meiosis) to distance from the centromere in this situation.\textsuperscript{10,23} Fortunately, all models agree that a very low level of heterozygosity (less than 20%) would only be expected within a short distance (<20 cM) from the centromere. From table 1 it is clear that the only locus falling within this region is PGM3, and here a high proportion of homozygous teratomas would be expected and was indeed observed.

However, at the other loci there are far fewer heterozygotes than expected, there being only three examples of heterozygosity out of 35 chances among tumours known to be homozygous for centromere markers. One explanation for this would be a reduced frequency of crossing over in meiosis leading to ovarian teratomas. This seems inherently rather unlikely since the amount of crossing over is determined during fetal life, so that it would be necessary to postulate an abnormality in some of the primary oocytes at a very early stage. We have also recently obtained direct evidence that crossing over does occur in oocytes destined to become teratomas from detailed studies on one of the cases described here (DC 131).\textsuperscript{24} The results confirmed the existence of crossing over in the short arm of chromosome 1 in all seven teratomas before development.

A low level of heterozygosity together with clear evidence of crossing over therefore suggest to us that a substantial number of teratomas do not arise by failure of meiosis II. This contrasts with the situation in the inbred mouse line LT/Sv where elegant experiments using teratomas in recombinant inbred strains have given gene-to-gene map distances comparable with those obtained by classical backcross analysis.\textsuperscript{25} This provides strong evidence that in the mouse these tumours can arise after suppression of meiosis II. The gene-to-centromere distances estimated from the teratomas were rather less than those obtained using Robertsonian translocations and pedigree analysis. Although this could possibly represent a small admixture of teratomas of different origin, the authors' suggestion that Robertsonian translocations may change the frequency of crossing over seems more probable.

\textbf{ATTEMPTED DIVISION OF A MATURE OVUM (FIG 5 III)}

If some stimulus caused an ovum to reach maturity within the ovary and then to attempt to divide but the first cleavage was not successful, this would result in a doubling up of the haploid chromosome number. All chromosome and enzyme markers would then be homozygous. The results on 11 of the 13 teratomas homozygous at the centromere would be compatible with this mode of origin.

\textbf{FUSION OF TWO INDEPENDENTLY DERIVED MATURE OVA}

In a heterozygous patient there would be an equal chance of homozygosity or heterozygosity at each locus. Some centromere markers might be heterozygous and others homozygous in the same tumour. This was never found in our series, but this mode of origin cannot be formally excluded in any particular case.

\textbf{FERTILISATION}

This would produce tumours containing genes and chromosome markers not present in the patient. This was not seen in any case.

The most likely interpretation of our results seems to be that the development of a teratoma is associated with an attempt to complete the whole of meiosis, and indeed to continue into development of a zygote, within the ovary and without the stimulus of fertilisation. In this abnormal environment there is a failure of the products of cell division to separate, and this can occur at several different stages giving tumours of different genetic constitution. The trigger for these precocious divisions is quite unknown. From a practical point of view, the heterogeneous nature of these ovarian teratomas makes them completely useless for human gene mapping. Even if extensive testing established the mode of origin in a particular case, considerable bias would be introduced in this way. However, the results do reawaken questions about the biology of germ cells and their tumours.

It is of interest that, even with hindsight, we can detect no morphological differences between tumours thought to arise in these different ways. It has been suggested that the benign nature of teratomas may be a reflection of their heterozygous genotype.\textsuperscript{26} However, many of the benign tumours described here are apparently completely homozygous. In contrast, malignant testicular teratomas show heterozygosity with respect to enzyme markers, centromeres, and the possession of a Y chromosome\textsuperscript{27}(and our unpublished observations).

We cannot, of course, make any deduction from the birth of an infant with trisomy 21 to one of the patients with bilateral dermoid cysts. We could not, however, exclude any association between these different meiotic errors, and are not aware of any published data on this subject.

If our interpretation of the origin of ovarian teratomas is correct, it is curious that duplication of a
haploid genome arising maternally in the ovary produces a dermoid cyst, whereas duplication of a sperm genome growing in the uterus gives another benign tumour, the hydatidiform mole.28 29 It would be of interest to examine the origin of the rare malignant ovarian teratomas, as well as other germ cell tumours, from the same point of view.

We are most grateful to Professor Fairweather and his colleagues, all the theatre staff at the National Temperance hospital, and Dr P Hughesdon (pathologist) for their patience and co-operation over many years. The expert technical assistance of Gloria Jones, Steve Jeremiah, and Nona Parry-Jones were also appreciated.

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