Pathogenesis of intracranial germ cell tumors reconsidered

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**Object.** To determine the pathogenesis of intracranial germ cell tumors (GCTs), the author studied 153 cases of these tumors encountered through 1994, 62.7% of which showed monotypic histological patterns and 37.3% of which were shown to be mixed tumors.

**Methods.** Six patients died soon after admission and underwent autopsy; the other patients underwent surgery followed by radio- and/or chemotherapy. One hundred thirty-four cases were followed through the end of 1997. All patients with a choriocarcinoma died within 1 year. Patients with a yolk sac tumor (endodermal sinus tumor) or an embryonal carcinoma also had poor outcomes. Patients with a mature teratoma had 5- and 10-year survival rates of 93% each. Patients with an immature teratoma had 5- and 10-year survival rates of 86% each, whereas patients who had a teratoma with malignant transformation had a 3-year survival rate of 50%. Patients with a germinoma had a 5-year survival rate of 96% and a 10-year survival rate of 93%. These results may bring into question the validity of the germ cell theory because germinoma, which should be the most undifferentiated tumor according to the theory, was the most benign and choriocarcinoma and yolk sac tumor (endodermal sinus tumor), which should be the most differentiated tumors, were the most malignant according to results obtained during the follow-up study.

**Conclusions.** Germ cell tumors other than germinomas may not originate from one single type of cell (primordial germ cells). The embryonic cells of various stages of embryogenesis may perhaps be misplaced in the bilaminar embryonic disc at the time of the primitive streak formation, becoming involved in the stream of lateral mesoderm and carried to the neural plate area to become incorrectly enfolded into the brain at the time of neural tube formation. The author propounds the following hypothesis: tumors composed of cells resembling the cells that appear in the earlier stages of embryogenesis (ontogenesis) are more malignant than those composed of cells resembling the cells that appear in the later stages of embryogenesis.

**KEY WORDS** embryogenesis • germinoma • germ cell tumor • survival rate

Germ Cell Tumors: What Are They?

My colleagues and I have asserted that there are two types of intracranial (particularly pineal) two-cell pattern tumors: germinoma, which displays positive immunohistochemical staining for placental alkaline phosphatase, and pineocytoma with lymphocytic infiltration, which demonstrates negative staining for placental alkaline phosphatase. Zülch has reported that these two types of two-cell pattern tumors can be differentiated by Di Girolami impregnation and periodic acid–Schiff staining. Despite divergent views such as these, the trend now is in favor of denying the duality of the two-cell pattern tumors and affirming the germ cell origin of all these tumors.

Therefore, under the term “germ cell tumors” (GCTs), whether gonadal or extragonadal, it is now customary to include germinoma (seminoma or dysgerminoma), mature and immature teratoma, malignant teratoma or teratoma with malignant transformation, embryonal carcinoma, yolk sac tumor (endodermal sinus tumor), choriocarcinoma, and so-called mixed GCTs (tumors consisting of two or more of these tumor components). This classification, based on the “germ cell theory,” maintains that these tumors originate from germ cells. Whether the “germ cells” correspond to the primordial germ cells known in embryology or to certain stages of differ-
entiation of the primordial germ cells is not clear. Takei and Pearl adopted the concept of totipotent malignant germ cells posited by Mostofi and proposed a schema of possible oncological phylogeny of GCTs.

The primordial germ cells, first recognized in the normal embryonic yolk sac endoderm, migrate toward the gonadal folds. Germ cells that are topographically misplaced during migration normally do not survive and are probably eliminated by an immune mechanism. If they survive and acquire neoplastic properties as a result of unknown oncogenic factors or mutant genes, they may be designated as “neoplastic germ cells with totipotentiality.” An analogous oncogenesis may occur within the gonadal folds, which are the normal destination of the migrating primordial germ cells. Such neoplastic germ cells have been found and referred to as “intratubular malignant germ cells.”

According to Takei and Pearl, germinomas (seminomas and dysgerminomas) are formed by neoplastic germ cells without further differentiation. The interspersed lymphocytes in germinomas probably arise from an immune response to the neoplastic germ cells and may play a role in preventing their further differentiation. The totipotent neoplastic germ cells may mature along either embryonal or extraembryonal lines. Embryonal differentiation results in teratomatous elements. Along an extraembryonal line, trophoblastic differentiation results in the formation of a choriocarcinoma; the other line of extraembryonal differentiation is toward the yolk sac tumor (endodermal sinus tumor) and embryonal carcinoma. The major structural difference between the two is that an embryonal carcinoma is predominantly composed of anaplastic endodermal cells, which are only one of multiple elements in a yolk sac tumor.

All of these theories seem to be based on a premise that GCTs, except for germinoma, arise by parthenogenetic fertilization of the germ cells. Is it possible that such parthenogenesis really occurs in the human body?

According to some pathologists, this parthenogenesis may seem to be self-evident. Ashley has suggested that there are two groups of teratomas. He writes, “One type seen in the gonads and possibly in the posterior abdominal wall is derived from germ cells by a process of parthenogenesis. The second type seen in the sacrococcygeal region, the head, and the chest is related to sequestration of cells of the blastula before differential blocking of the genome has occurred, and may be regarded as a derivative of an incomplete conjoined twin.” However, the intracranial teratomas that my colleagues and I have examined showed histological features similar to gonadal teratomas. According to the vast statistical data accumulated by the Brain Tumor Registry of Japan, an intracranial teratoma has two peaks in its age distribution: the first peak is in the neonatal and infancy period (10.4%) and the second peak is in the childhood period between 5 and 14 years of age (48.1%). It may be possible that teratoma in the first peak may be regarded as fetus-in-fetu and teratoma in the second peak derives from germ cells. This theory, however, has no proof. Arias-Bernal and Jones studied chromosomes of a malignant ovarian teratoma. They commented, “the finding of chromosomes in the near diploid range again fails to support the idea that teratomas are possibly of germ cell origin in the ovocyte stage after chromosome reduction” and “if teratomas arise from germ cells, it is likely that the origin in the ovary, at least, is from a cell in the oogonium stage, or even earlier. It does not seem necessary to invoke the concept of par-

Fig. 1. Diagram depicting the germ cell theory, showing the twisted, improbable pathogenetic lines. (Reprinted with permission of Sano K: So-called intracranial germ cell tumours: are they really of germ cell origin? Br J Neurosurg 9:391–401, 1995.)
contradicts the axiom of general oncology that the more undifferentiated a tumor is the more malignant it is and that the more differentiated a tumor is the more benign it is. To solve this contradiction, we propose working hypotheses in the subsequent section.

**Personal Experiences With Intracranial GCTs**

**Statistical Results**

Through 1994, 153 cases of histologically verified intracranial GCTs were studied as reported previously.\(^5\) We excluded from the study some of the two-cell pattern tumors in the pineal or suprasellar (neurohypophysis) region that we thought were tumors of pineal parenchyma origin (pineocytoma with lymphocytic infiltration) according to criteria stated elsewhere.\(^3\) Ninety-six cases (62.7%) displayed one type of histological composition in 98% or more of the examined sections, such as mature or immature teratoma, teratoma with malignant transformation, germinoma, embryonal carcinoma, yolk sac tumor (endodermal sinus tumor), and choriocarcinoma. Fifty-seven cases (37.3%) were the so-called mixed GCTs (49 cases) or germinoma with syncytiotrophoblastic giant cells (STGCs) (eight cases). The mean patient age was 16.1 ± 8.1 years. In 78 cases (51%) the tumors were located in the pineal region, in 46 cases (30%) in the neurohypophysis (suprasellar) region, in 16 cases (10.5%) in other areas, and in 13 cases (8.5%) in multiple locations. There were 122 males (79.7%) and 31 females (20.3%) (male/female ratio 4:1).

Mixed GCTs were composed of various combinations of two or more types of GCTs. Germinoma and teratoma components were most frequently seen. In the whole group of mixed GCTs, germinoma components were found in 79%, teratoma components in 63%, yolk sac tumor components in 33.3%, and embryonal carcinoma components in 15.8%.

Patient gender and tumor location distribution of GCTs were interesting. Among 78 tumors located in the pineal region, 76 were found in males and only two in females, whereas in the neurohypophysis (suprasellar) region 21 tumors were found in males and 25 in females. Therefore, there was a pronounced male predominance of GCTs in the pineal region and a slight female predominance of GCTs in the neurohypophysis region.

It is well known that occipital encephalocele is predominant in females.\(^3\) This may suggest that closure of the anterior neuropore occurs later in females than in males. If so, enfolded embryonic cells may reach deeper in the midline (neurohypophysis region) in females than in males, and those cells in males may reach a shallow part of the neural tube, that is, in the pineal region. This may explain the findings of male predominance of GCTs in the pineal region and a slight female predominance of the tumors in the neurohypophysis region.

**Survival Rates of Patients With GCTs**

The survival rates (using the Kaplan–Meier method) in our series of patients with so-called intracranial GCTs treated by surgery, postoperative radiation therapy, and/or chemotherapy were shown in our previous papers\(^12,15\) and reinvestigated in December 1997 (Table 1). All patients
Pathogenesis of germ cell tumor

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<th>Survival rates in 134 patients with so-called germ cell tumors*</th>
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<td>Tumor Histological Type</td>
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* Malign transform = malignant transformation; MXB = mixed tumor mainly consisting of germinoma or teratoma with a small portion of malignant tumor; MXM = mixed tumor mainly consisting of choriocarcinoma, embryonal carcinoma, or yolk sac tumor; NC = could not be counted.

with a choriocarcinoma, an embryonal carcinoma, or a yolk sac tumor demonstrated the lowest survival rates and the tumors were therefore malignant, whereas patients with a germinoma or a mature teratoma had longer survival rates (10-year survival rates of 93% each) and their tumors were benign. Survival rates for patients with an immature teratoma or a germinoma with other components (such as STGCs) fell between the rates of the malignant and benign groups. These data contradict the germ cell theory according to which choriocarcinoma and yolk sac tumors are the most differentiated and should be the most benign.

### Pathogenetic Mechanisms of GCTs

**Hypothesis I. Nature of Tumors: Histogenetic Stages Compared With Ontogenetic Stages**

As is well known, in the Bailey–Cushing classification of gliomas or neuroectodermal tumors, those composed of cells resembling the cells in earlier stages of histogenesis are more malignant than those resembling the cells in later stages of histogenesis. However, in so-called GCTs, we may assume the following based on our experiences: tumors composed of cells resembling the cells that appear in earlier stages of embryogenesis (ontogenesis) are more malignant than those composed of cells resembling the cells that appear in later stages of embryogenesis.

Each of the so-called GCTs may represent the neoplastic equivalent of an embryonic stage of development (Fig. 2): the trophoblast (choriocarcinoma) that appears as early as in the stage involving blastocyst formation, the yolk sac
endoderm (yolk sac tumor or endodermal sinus tumor), the pluripotent stem cell of the embryo proper (embryonal carcinoma), the embryonic differentiated cell (teratoma), and the primordial germ cell (germinoma). With the exception of the germinoma, these tumors may not originate from one single type of cell, namely, the primordial germ cell.

Therefore, the true GCT may be only one: germinoma. The other so-called GCTs should be regarded as enfolded cell–derived dysembryogenetic tumors as stated later.

Hypothesis II. Incorrect Involvement and Enfoldment

In 1882, Cohnheim propounded a theory of tumorigenesis in which neoplasms develop from the embryonic cell rests (embryonale Anlage, or “verirrte Keime”) that do not participate in the formation of normal surrounding tissues and are alien to the environment, defying its physiological regulation (note: deregulated growth is one of the main characteristics of neoplasms). This older theory may still hold true for dysembryogenetic or malformative tumors. For instance, craniopharyngioma is believed by many authors to arise from the epithelial cell rests of Rathke’s pouch; that is, this tumor is thought to be derived from the embryonic cell rests in situ. No such embryonic cell rests corresponding to each of the so-called GCTs normally exist in the cranial cavity.

Why these tumors arise in the cranial cavity may be explained by the “misinvolvement–misenfoldment” hypothesis. At the end of the 1st week of embryogenesis, implantation of the blastocyst into the uterine wall commences and trophoblasts start proliferating rapidly. In the beginning of the 2nd week, the bilaminar embryonic disc is formed from the inner cell mass of the blastocyst. The embryonic disc is closely attached to the cytotrophoblast, the syncytiotrophoblast, the amnion cells, and the yolk sac (primary and secondary) endoderm at its lateral margins (Fig. 3) so that cells of these structures may be misplaced in the disc edges. In the beginning of the 3rd week of embryogenesis, the primitive streak appears at the caudal portion of the embryonic disc, formed by the movement of proliferating embryonic disc cells toward the midline entering the primitive groove. These cells leave the basal layer of the primitive groove, migrate laterally between the embryonic ectoderm and endoderm, and become organized into a layer called the intraembryonic mesoderm. Some misplaced cells of the embryonic disc, such as those of the adjacent yolk sac endoderm, the trophoblastic layer, or the amnion (produced by the cytotrophoblast), may be involved in this movement and migrate with the moving cells of the mesoderm, especially the lateral mesoderm, to the future cranial area (“misinvolvement”) (Fig. 4). At approximately the 18th day, when the neural plate is formed and starts folding to form the neural tube, these migrated cells may be enfolded into the neuraxis (“misenfoldment”), and from these cells the previously mentioned so-called GCTs may later develop. The primordial germ cells first recognized as such by the end of the 3rd week (the 21st day) or the beginning of the 4th week (the 22nd day) in the yolk sac endoderm and near the origin of the allantois should be already present in the yolk sac endoderm before that date and may migrate with lateral mesoderm cells to the neural plate area where they are misenfolded into the neuraxis and give rise to a germinoma. It is also possible that the primordial germ cells, during their physiological migration to the gonadal ridge, may be involved in a group of moving lateral mesoderm cells and
that are distributed to wide areas of the embryonic disc, especially along its midline, beside the neural plate where they may be enfolded into the neuraxis.\textsuperscript{22,23} The existence of mixed GCTs of various combinations of cell components can also easily be understood. The recently described combination of germinoma and STGCs\textsuperscript{29,31} can be interpreted as follows: the syncytiotrophoblastic cells and the primordial germ cells (yolk sac endoderm cells) are involved together in the lateral mesoderm stream moving to the future cranial area and are misfolded into the cranial cavity. In these tumors, cytotrophoblasts are not present, whereas in choriocarcinoma or mixed tumors with choriocarcinomatous cells, STGCs, which probably derive from cytotrophoblasts, are seen. The existence of a germionoma with STGCs without cytotrophoblastic cells may indicate that the coexistence of germinoma and syncytiotrophoblastic cells is only incidental (incidental misinvolvement). Most of these misinvolved cells are probably destroyed by immune mechanisms of the body, and only a small percentage of the cells reach the cranial cavity.

Figure 2 again shows the relationship between each stage of the embryonic development and expectant neoplasms that will arise from misinvolved–misenfolded cells. This schema can explain the diversity of so-called GCTs and their nature (grades of malignancy). There is no reason to believe that all these tumors must be attributed to one single origin, the primordial germ cells, as shown in Fig. 1, which illustrates the twisted, improbable pathogenetic lines.

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