THE THREE TYPES OF GLIOBLASTOMA

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The problem of glioblastoma multiforme is an ever present one in the neurosurgical clinic. In Cushing's material of intracranial tumors the glioblastomas amounted to 10.4 per cent. While the problem therefore is of importance numerically, problems of diagnosis, of treatment and of purely human consideration are no less. In some clinics the tendency has been to give up, as far as this group of tumors is concerned, and the surgical problem has been transformed into a purely diagnostic one. It was hoped that the demonstration of arteriovenous anastomoses by angiography (Tönnis) would aid the diagnosis, but it was soon found that this sign was present in only a certain number of cases.

In the Copenhagen clinic we have followed the principle of always operating in these cases whenever the general state of the patient allowed it—in the first years because we felt that our experience was too meagre to warrant a certain diagnosis, and later on because it became apparent that some patients with glioblastoma had a sufficiently long useful survival to justify operation. Growing experience seemed to show that long postoperative survivals were combined with certain macroscopical and microscopical features, and in this report we have tried to correlate these findings for the glioblastomas in our first 1000 intracranial tumors—102 patients. In the pathological report and in some tables, 31 later cases have been added. The survival periods and the pathological findings were not compared until the two parts of the work were finished.

PATHOGENESIS

The gliomas commonly are thought to be ectodermal tumors caused by dysontogenetic factors, some cells arrested at an embryonal stage becoming mother cells of the tumors. Ostertag and others have shown that even in the normal subject unripe cells are to be found in certain localizations, e.g. the gyrus cinguli and the corpus callosum, where glioblastomas frequently occur. The factors which "set off" the cells to sudden blastomatous growth are, however, unknown. In some gliomas, moreover, processes of both differentiation and of de-differentiation occur and a polymorphous or "multiform" picture is found, as in the glioblastomas. The marked degeneration phenomena, the fact that glioblastomas never metastasize and the rapid explosive growth have led some to assume that the glioblastomas really are degenerative processes and no true tumors at all.

In 1938 to 1944 Einarson and Neel, and Einarson, Neel and Strömgren in a series of papers put forward a working hypothesis which may make it possible to combine the two theories and which may bring the solution.
THREE TYPES OF Glioblastoma

Working on the different forms of diffuse sclerosis, diffuse gliomatosis and glioblastomatosis they found that the differences might be due to varying constellations of the same four factors:

1. The dystrophic tissue factor: a constitutional insufficiency of the interfascicular oligodendroglia in dealing with the nutrition of the myelin sheaths.

2. The dyscatabolic tissue factor: an insufficiency of the microglia in dealing with the abnormal metabolic prelipoids and degeneration products of the myelin sheaths.

3. The histochemical tissue factor: the biological (stimulating resp. inhibiting) actions of the atypical metabolic degeneration products on the astrocytic apparatus.

4. The dysplastic tissue factor: the individual inherent tendency of the macroglia to proliferation and blastomatous growth.

Most probably the dystrophic factor is a hereditary condition sine qua non for the development of the vast demyelinization characteristic of diffuse sclerosis (recessive inheritance). Based on this tissue factor hypothesis the authors introduced a new quantitative-histological classification of the cases of diffuse sclerosis.

The causal release of the first three tissue factors is thought to take place through influences exogenous to the brain (infections, trauma, intoxications, anoxia, dietary deficiencies, disturbances in lipid metabolism, endocrine anomalies, formation of a myelolytic agent). Furthermore the first three tissue factors are considered to possess the ability of actuating or releasing the fourth "intrinsic" tissue factor, and hence they may appropriately be termed "extrinsic." The use of these designations should, however, be strictly limited to this special conception. In their cases of diffuse glioblastomatosis the authors thus consider the intrinsic dysplastic factor the dominant one, while in other cases, characterized mainly by demyelinization and a milder form of reactive cellular gliosis, they think primarily of the 1st and 2nd factors, the 3rd factor only secondarily stimulating the cells to blastomatous growth. Only then does the 4th factor become of importance; in glioblastomatosis it is "intrinsic" with respect to the others.

An apparently significant argument in favor of this theory is the authors' claim to have definitely established the true existence of a glioblastomatous form of diffuse sclerosis, and to have shown that there actually do occur transitional cases between diffuse sclerosis (a degenerative process) and diffuse glioma (a true tumor); we refer especially to their Cases 7 and 8 (Einarson and Neel) and Case 13 (Einarson, Neel and Strömgren).

While this theory—or rather synthesis of theories—cannot as yet be considered proven, there are so many points which seem relevant to our problem that this short summary seems justified.

PATHOLOGY

While some authors have subdivided the classical glioma groups of Bailey and Cushing, others have tried to simplify this grouping. Thus, Bergstrand...