Aglyco Pathology of Viral Receptors in Dementias

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Six previously isolated sets of studies have been brought together to define a condition we have named *aglyco pathology*[a]: (1) Glycoconjugate receptor structures in brain are known sites for viral attachment, and influenza viral neuraminidase cleaves neuraminic acid from glycoreceptors during virus entry into the cell. Thus, for example, brain gangliosides *in vitro* were shown to act as receptors for influenza virus, and *in vivo* additional gangliosides administered intracerebrally acted as a "decoy" and inhibited infection of brain neurons by influenza virus.[1–7] (2) Quantitative neurochemical studies suggested that covalently bound neuraminic acid (NA) and hexosamine (HA) in brain normally are part of a glycoconjugate intercellular recognition "sign-post" system, which forms the neural networks underlying normal brain development and behavior.[8,9] (3) A quantitative decrease in glycoconjugates, in conjugated NA and HA, occurs in schizophrenia.[10–25] That nondialyzable conjugated NA and HA in cerebrospinal fluid (CSF) are quantitatively decreased in schizophrenia is here confirmed in a double-blind study. (4) Recent epidemiological studies indicate that infection prenatally with influenza virus predisposes to schizophrenia.[26–28] (5) Recent histological and brain-scan studies in schizophrenia reveal neuronal loss.[29,30] (6) An example of aglyco pathology has been demonstrated in glioblastomas, in which the decrease of carbohydrate in the glycoconjugate brain glycoprotein 10B exposes epitopes in a constituent peptide of 10B called malignin; these epitopes in turn induce a quantified cytotoxic auto-antibody response, anti-malignin antibody (FIG. 1), with resultant destruction of the cells containing the newly exposed epitopes at picograms of antibody per cell.[31–33] This mechanism operates in other malignancies as well (FIG. 1). It is proposed that neuronal cell loss in dementia praecox (schizophrenia) and other dementias, such as those which occur in Alzheimer's disease and parkinsonism, is produced by similar aglyco pathology of viral receptors.

Aglyco pathology can be detected by quantitative determination either of the altered glycoconjugates themselves or of the cytotoxic antibody which is produced against the newly exposed epitopes. The quantitative determination of the altered glycoconjugates themselves is demonstrated in schizophrenia (FIG. 2). To be described in detail elsewhere, CSF from schizophrenic and nonschizophrenic patients at the National Institute of Mental Health, Bethesda was shipped blind in dry ice to the Foundation for Research on the Nervous System in Boston where conjugated NA and HA were determined. Each of the specimens was lyophilized, dialyzed

[a] Aglyco is a trademark of Aglyco, Inc.

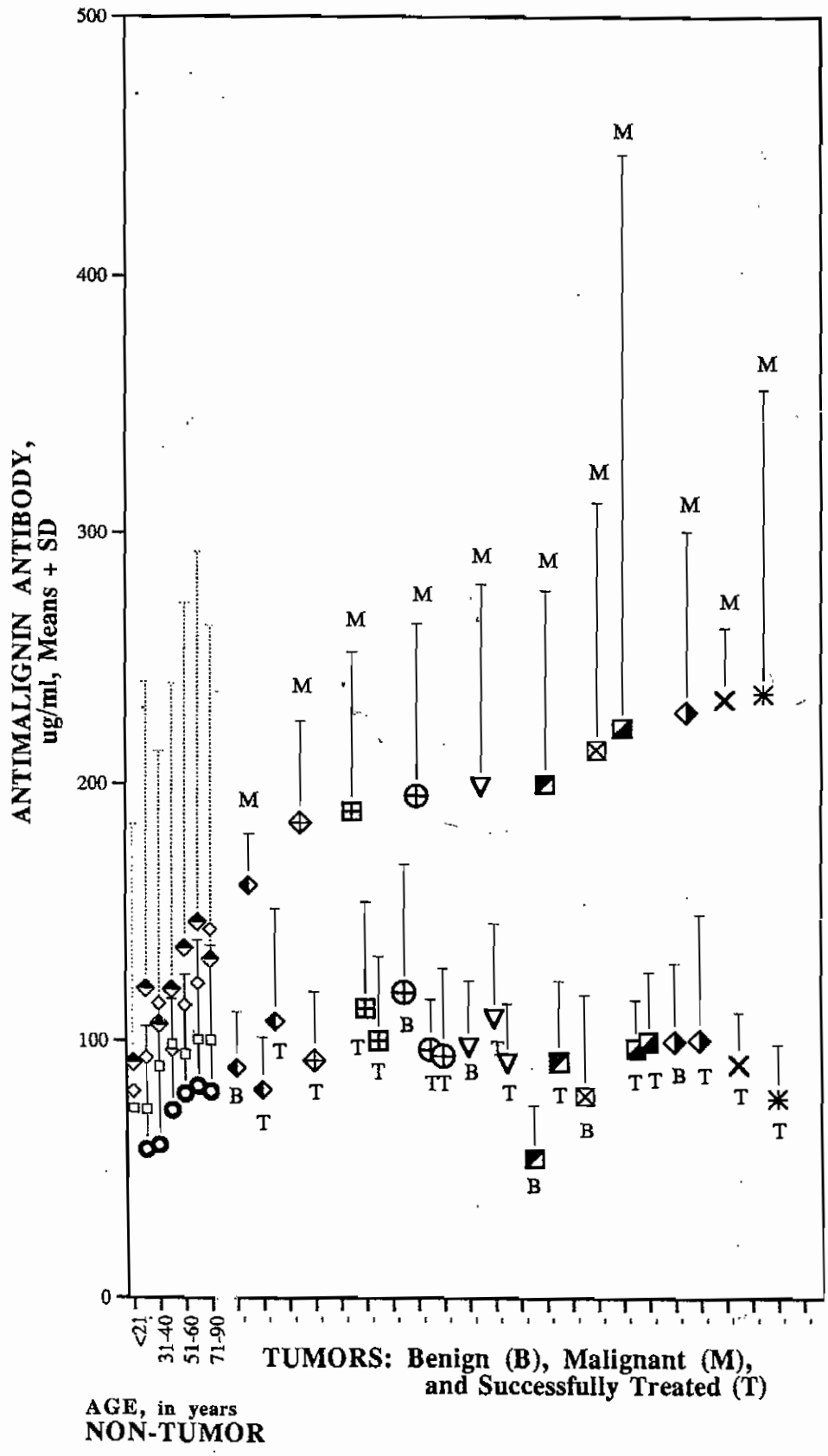
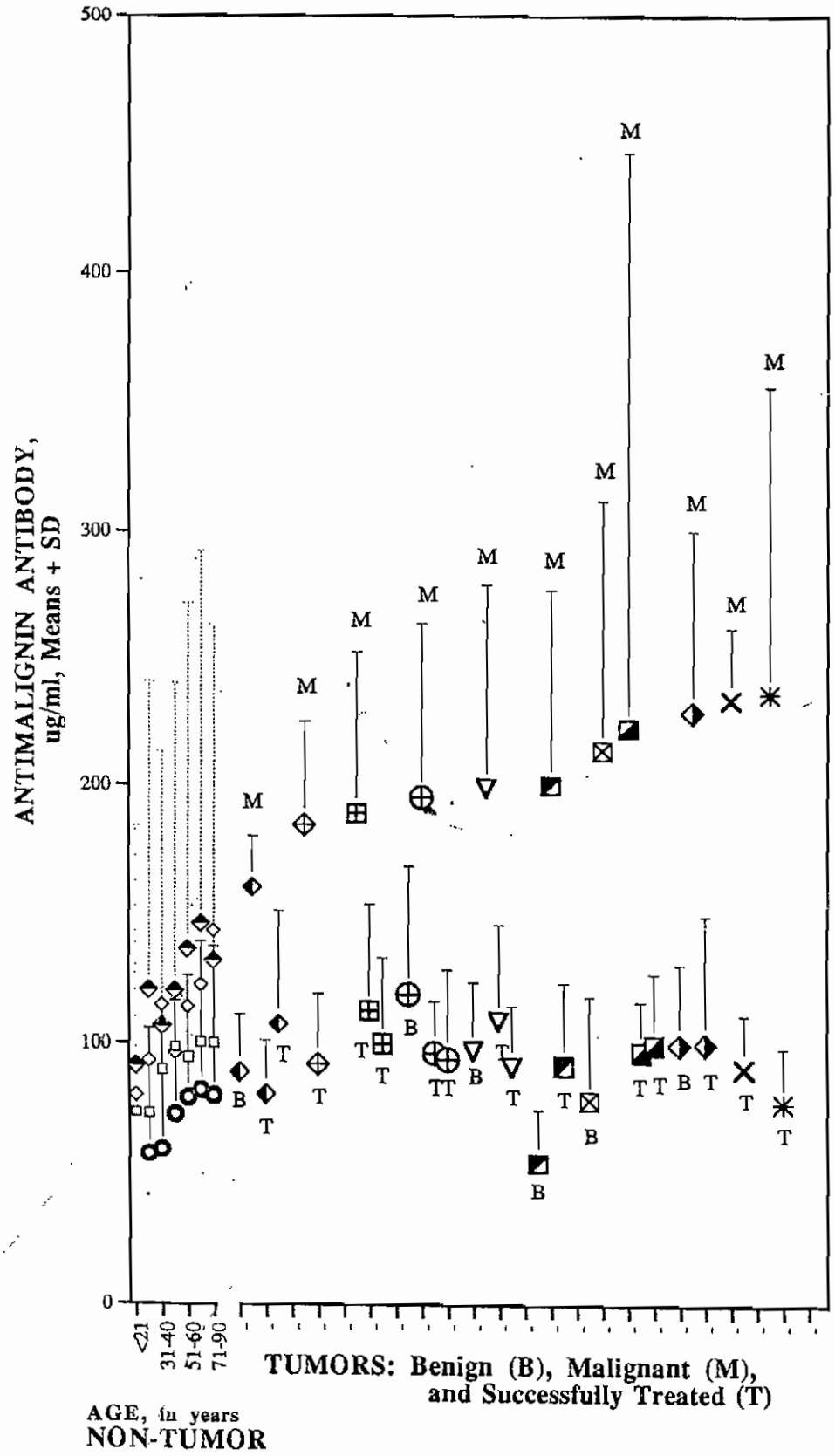


FIGURE 1. Antimalignin antibody in non-tumor and tumor populations. Number in each group appears in parentheses. **Non-tumor:** ○ Normal healthy controls (1,972); □ Screen: Unknown family history (732); ◇ Screen: +ve Family history, asymptomatic (193); ◇ Screen: +ve Family history, symptomatic (181). **Tumor:** ◇ Ovary (58); ◇ Melanoma (20); □ Colorectal (99); ○ Breast (600); ▽ Prostate (80); ◩ Genitourinary (47); ⊠ Brain (104); ◪ Lung (62); ◆ Uterus (46); ✕ Basal cell, skin (11); ✳ Lymphoma-leukemia (73). **Total number: 4,278.**



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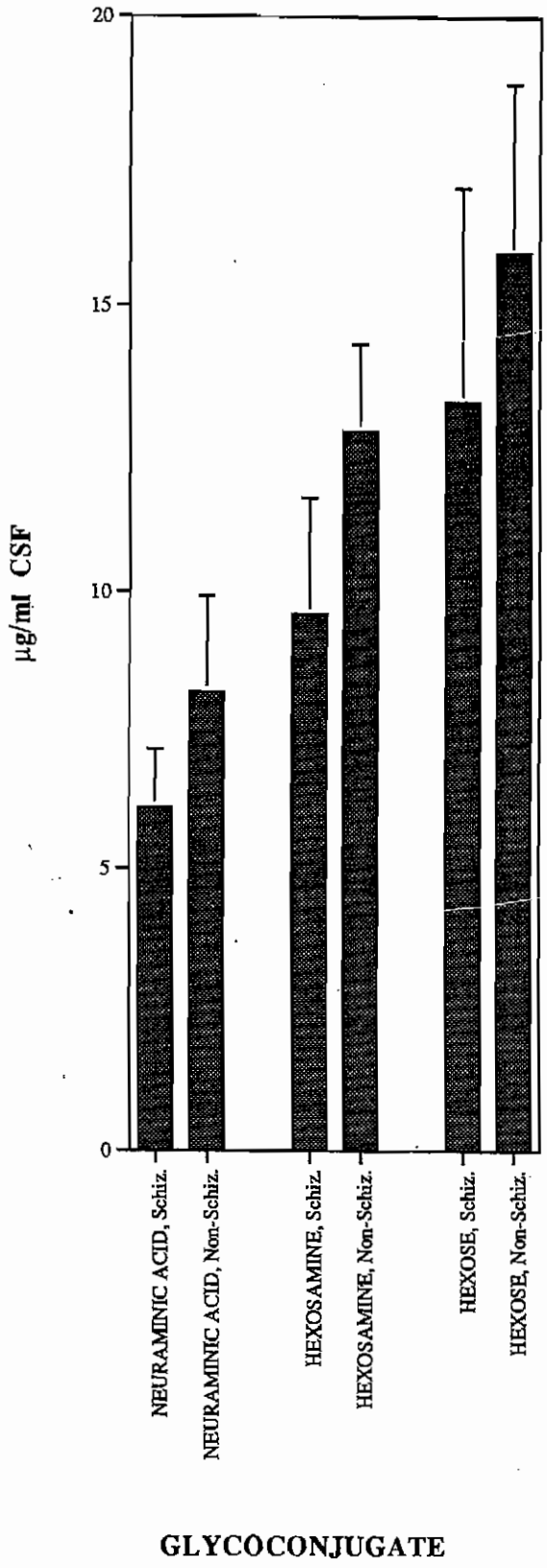

FIGURE 2. Glycoconjugate neuraminic acid, hexosamine, and hexose, in cerebrospinal fluid (CSF) of schizophrenic (Schiz.) and nonschizophrenic (Non-Schiz.) patients, in µg/mL CSF, mean ± SD.

against distilled water exhaustively (cellophane pore size approx. MW 12,000 Da) at 0–5 °C to remove free NA and free hexose, and the nondialyzable fraction was quantitatively analyzed in duplicate for conjugated NA by the Bial's orcinol method and the thiobarbituric acid method (again shown to be unreliable), and for conjugated HA and glucose as previously described.[10–25] After the neurochemical tests were completed, the code was broken. The results are shown in FIGURE 2. Conjugated NA ($p < 0.025$; 81.8% of the schizophrenic group <7.5 μg/mL; 83.3% of the nonschizophrenic group >7.5 μg/mL) and conjugated HA ($p < 0.006$), but not conjugated hexose, were statistically significantly lower in concentration in the schizophrenic than the nonschizophrenic group.

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Diversity of Interacting Receptors

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