tion, when rat 2 was subsequently tested under hunger rather than stimulation, he used either eye equally well.

As neither the brain stimulation nor the response requirement changed when the light was switched from right to left, the change in response rate must be due to a difference in sensitivity to stimuli. This result confirms that the contralateral facilitation produced by stimulation is at least partially a sensory (input) effect.

This, of course, does not mean that the hypothalamus exerts only sensory control. Turner (*6*) concluded, on the basis of lesion-produced deficits in conditioned escape, that he had destroyed tissue that normally connected sensory and motor systems. As the animals in our experiment were not constrained to use one paw exclusively, the results do not bear on the issue of possible motor effects. We have observed, however, that rats trained to press a lever generally prefer one paw over the other regardless of which side of the hypothalamus is being stimulated or which eye sees the light signal.

The evidence we have presented supports the conclusion that hypothalamic stimulation produces functional behaviors such as eating and drinking in part through altering the animal's sensitivity to the sensory stimuli that trigger them (*7*). It also demonstrates that lateralized sensory facilitation produced by stimulation is not limited to the control of reflexes or stereotyped actions, such as orientation or biting, but can also affect the performance of a learned response.

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References and Notes

1. R. Bandler and J. P. Flynn, *Science* **171**, 817 (1971).
2. J. F. Marshall and P. Teitelbaum, *J. Comp. Physiol. Psychol.* **86**, 375 (1974).
3. Techniques of electrode implantation and stimulation were similar to those reported in W. K. Beagley, *ibid.* **90**, 790 (1976).
4. The bulbs were 9 mm by 4 mm in diameter, 1.5 volts (Edmund Scientific Co., Barrington, N.J. 08007).
5. R. D. Lund [*Science* **149**, 1506 (1965)] reported very few uncrossed visual fibers in the albino rat. Thus, most of the input to one eye crosses to the opposite side of the brain.
6. B. H. Turner, *J. Comp. Physiol. Psychol.* **82**, 37 (1973).
7. H. Vanegas, W. Foote, J. P. Flynn, *Yale J. Biol. Med.* **42**, 191 (1970); D. A. Smith, *Physiol. Behav.* **8**, 617 (1972).
8. Conducted at Emory University and supported by the Emory University Research Committee. We thank G. Beagley and J. deGive for technical help.

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Alzheimer's Disease, Trisomy 21, and Myeloproliferative Disorders: Associations Suggesting a Genetic Diathesis

Abstract. *Relatives of probands with Alzheimer's disease had excessive incidences of trisomy 21 and myeloproliferative disorders. Microtubules are structures that are likely to be affected by a genetic defect causing a predisposition to Alzheimer's disease, trisomy 21 and, possibly, to myeloproliferative disorders.*

Among 301 first-degree and 556 second-degree relatives of 30 probands with histopathologically proven Alzheimer's disease, 22 had Alzheimer's disease, 6 had trisomy 21 (Down's syndrome, mongolism), and 13 had a myeloproliferative disorder. The incidence of trisomy 21 and myeloproliferative disorders is notably excessive compared to what one would expect in a general population (Table 1). Alzheimer's disease has a known genetic component (*1*). The morbid risks to relatives found in this study (parents 0.23 ± .07 and siblings 0.10 ± .04) are higher than those previously reported, probably because the number of probands with histologically proven disease was much larger in this study and the search for secondary cases was intense. The evidence adds to a set of relationships implicating a single genetic defect in the etiology of some proportion of all three disorders and suggests faulty organization of microtubules as a cause of the pathology.

Alzheimer's disease is one of the presenile dementias present in about 70 per 100,000 persons over age 40 dying in Minnesota (*2*). Starting in late middle age the victim exhibits a loss of memory for recent events, and this decline in mentation relentlessly progresses until a vegetative state is reached. The cases of Alzheimer's disease for this study came from a series of 2204 consecutive autopsies done between 1952 and 1972 in Minnesota state hospitals and a state nursing home. Brain tissue changes characteristic of Alzheimer's disease were found in 30 persons: 12 males and 18 females whose illness began before age 65. The mean age of onset was 55.9 years, the remaining life expectancy was 7.9 years, and all were of North European origin.

From their relatives and from records, a medical history was obtained for the probands' parents, siblings, and children, and for all relatives of probands and their siblings through second-degree genetic relationships to an affected person (proband or relative who had Alzheimer's disease). At least one interview was conducted per family and there were usually four or five interviews. All birth and death certificates and medical records were reviewed. Special effort was directed at obtaining autopsy results or obtaining autopsies of relatives who died while the study was in progress.

In 6 of the 22 relatives with Alzheimer's disease, the disease was confirmed by autopsy. Diagnoses for 11 cases were based on medical records and, for five cases, on family history. All cases of trisomy 21 were diagnosed in medical facilities. In two cases a karyotype demonstrated the trisomy and in four cases the diagnosis was based on clinical evidence. A clinical diagnosis of trisomy 21 is based on relatively unambiguous physical criteria and is considered quite valid. However, the possibility of translocations and mosaics causing the disorder cannot be excluded. In addition, five persons, all deceased, had phenotypes suggesting autosomal aberrations, and there was an excess of neonatal deaths [from 50 to 300 percent depending on the group used for comparison (*3*)]. These findings suggest that aberrations other than trisomy 21 were present in excess.

All of the myeloproliferative disorders were diagnosed in medical facilities, although in four cases the only written rec-

Table 1. Expected and observed incidences of trisomy 21 and myeloproliferative disorders among relatives of 30 probands with Alzheimer's disease (*14*).

Disorder	Persons at risk	Number of cases		*P**
		Expected	Observed	
Trisomy 21	777	1.20	6	< .0001
Myeloproliferative disorders				
First- and second-degree relatives	837	5.90	13	< .01
First-degree relatives	301	3.06	10	< .001

*Probability of observed result or one more extreme.

ord available was a death certificate. Among first-degree relatives, one person had a myelogenous leukemia and in all the others the lymphatic tissues were involved: three had chronic lymphocytic leukemia, three had Hodgkin's disease, two had lymphosarcoma, and one had a lymphoma. The three myeloproliferative disorders among second-degree relatives were Hodgkin's disease, lymphosarcoma, and multiple myeloma. No myeloproliferative disorders occurred among the trisomy 21 cases and there was no overall excess of cancer. Because about half of the 196 deaths in persons at risk occurred before 1940, or were not medically attended, an adequate medical record was often not available and the frequency of all pathological conditions is probably underestimated.

Neuropathology is central to the interpretation of the evidence. In neurons from patients with Alzheimer's disease, bundles of microtubules which usually course smoothly through the cell constrict and twist at intervals of 800 Å, producing in the cytoplasm a tangled mass—the neurofibrillary tangle (*4*). An identical lesion occurs in the neurons of patients with trisomy 21, though it occurs when the patients are younger. During their fourth decade most persons with trisomy 21 develop a dementing illness with microtubular pathology indistinguishable under the light or electron microscope from that seen in Alzheimer's disease (*5*). Microtubules form the spindle that spatially orients chromatids and then, perhaps in association with actin, physically separates the chromatids during both mitotic and meiotic division (*6*). Thus a failure of microtubular organization provides plausible common ground between Alzheimer's disease and trisomy 21.

There are no evident relationships between microtubules or any other organelle and myeloproliferative disorders, yet there are good reasons to suspect a common pathological mechanism. The reasons are: (i) The frequency of leukemia is increased about 20-fold among persons with trisomy 21 (*1–9*). (ii) Leukemia is apparently increased among persons with other chromosomal aberrations (*10*). (iii) The proportion of myeloproliferative disorders found among first-degree relatives of probands with Alzheimer's disease was about the same as found among relatives of probands with a myeloproliferative disorder (*11*). (iv) There have been several reports of familial clustering of trisomy 21 and leukemia and of leukemia and lymphoma (*11*). (v) Most of the positive genetic findings in myeloproliferative disorders have involved chronic lymphocytic leukemia, and in this series 12 of the 13 cases were immunoproliferative (*11*).

Only 6 percent of the study population was known to be afflicted with any one of the three disorders. The 194 relatives of 10 probands had no instances at all of any of the three illnesses, and some of those probands may have been sporadic cases. In the remaining families sex-linked and recessive inheritance can be eliminated. Autosomal dominant inheritance with extremely low penetrance or multifactorial inheritance are each possible. No relation was found between the sex of the proband or age of onset of the proband's illness and the number of secondary cases. There were more male than female secondary cases but the difference was not statistically significant. The male to female ratios were, respectively: Alzheimer's disease, 15 : 7; trisomy 21, 4 : 2; myeloproliferative disorders, 5 : 8.

Finally, a relationship to aging runs through the evidence. Senile dementia features the same neuropathologic changes seen in Alzheimer's disease and is separated from Alzheimer's disease by only one criterion, age of onset. Onset before age 65 signifies Alzheimer's disease; onset after 65, senile dementia. Age of onset is an unsatisfactory delimiting feature, and evidence from this study and other analyses suggests that Alzheimer's disease is merely a premature and severe form of a malady that will affect most if not all of us provided we live long enough (*12*). In addition to age and the appearance of microtubular pathology in neurons, there is also the increased age of mothers of trisomic children and the similar relationship between age of mother and childhood leukemia, age and neoplasia, and the premature aging of persons with trisomy 21. Microtubules, so critical to so many activities of the cell, would be a likely target for genetically programmed aging and, at the other end of life, a degree of instability in microtubular organization might increase the likelihood of rapid evolution through chromosomal rearrangements.

Note added in proof: Wisniewski *et al.* (*13*) now describe the fibulary material in neurons undergoing the degeneration typical of Alzheimer's disease as a "bifilar helix" which may or may not be related to microtubules or microfilaments normally present in neurons.

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References and Notes

1. E. Slater and V. Cowie, *The Genetics of Mental Disorders* (Oxford Univ. Press, London, 1971), pp. 141–153. Appendix D discusses the Weinberg method for estimating the standard risks and standard errors used in this report.
2. L. L. Heston, *Arch. Gen. Psychiatry*, in press.
3. Twenty-five deaths in the first year of life occurred among the 777 persons born (32 per 1000). In a general Minnesota population 17 deaths would be expected on the basis of averaged 1936 and 1960 rates (22 per 1000). A parallel study of 3146 persons from families of probands with other dementing illnesses from the same autopsy series as the probands in this report yielded a death rate in the first year of ten per 1000 live births or eight deaths expected in the families of patients with Alzheimer's disease.
4. J. A. N. Corsellis, *Br. J. Psychiatry* (Spec. No. 9), 110 (1975); H. Wisniewski and R. D. Terry, *J. Neuropathol. Exp. Neurol.* **29**, 163 (1970).
5. W. G. Ellis, J. R. McCulloch, C. L. Corley, *Neurology*, **24**, 101 (1974); D. R. Crapper, A. J. Dalton, M. Skopitz, J. W. Scott, V. C. Hachinski, *Arch. Neurol.* **32**, 618 (1975).
6. J. R. LaFountain, *Biosystems* **7**, 363 (1975); J. R. McIntosh, Z. Cande, J. Snyder, K. Vanderslice, *Ann. N.Y. Acad. Sci.* **253**, 407 (1975).
7. W. Krivit and R. A. Good, *AMA J. Dis. Child.* **94**, 289 (1957); see also Lilienfeld (*8*, pp. 85–94). Leukemias of all types are reported among trisomy cases, not lymphomas or other solid tumors. However, the same cell types are involved and there is no reason to suppose that there are fundamental differences between lymphomas and leukemias, at least for the purposes of this report. There is a slight but definite tendency for trisomy 21 to run in families (*8*, pp. 75–77; *9*). Mothers of trisomic children are older than control mothers (*8*, p. 27), and so are mothers of leukemic children [E. A. Ager, L. M. Schuman, H. M. Wallace, A. B. Rosenfield, W. H. Gullen, *J. Chronic Dis.* **18**, 113 (1965); A. Stewart, J. Webb, D. Hewitt, *Br. Med. J.* **1**, 5086 (1958)].
8. A. M. Lilienfeld, *Epidemiology of Mongolism* (Johns Hopkins Press, Baltimore, 1969).
9. L. S. Penrose, *Br. Med. Bull.* **17**, 184 (1961).
10. R. W. Miller, *J. Natl. Cancer Inst.* **40**, 1079 (1968).
11. F. W. Gunz [*Ser. Haematol.* **7**, 164 (1974)] has reviewed the genetics of leukemia.
12. See (*2*). The issue is discussed by E. Zerbin-Rüdin, *Modern Prospectives in the Psychiatry of Old Age*, J. G. Howells, Ed. (Brunner-Mazel, New York, 1975); C. E. Wells, *Dementia* (Davis, Philadelphia, 1971), pp. 174–175; A. E. Slaby and R. J. Wyatt, *Dementia in the Presenium* (Thomas, Springfield, Ill., 1974), p. 66.
13. H. M. Wisniewski, H. K. Narang, R. D. Terry, *J. Neurol. Sci.* **27**, 173 (1976).
14. The numbers expected and at risk were computed from the following. Trisomy 21: 1 expected per 700 live births (*8*, pp. 16–19; *9*). This figure is probably high, however, and 1 in 1000 is more realistic [E. Zeuten, J. Nielsen, A. Nielsen, *Hereditas* **75**, 136 (1973)]. All persons born into the study population, except the parents of probands, were assumed to be at risk. Five trisomy 21 cases were found in second-degree relatives, one among first-degree relatives. Because most probands were born between 1890 and 1910, and their children were born between 1910 and 1940, adequately diagnosed cases of trisomy 21 could not really be expected among the probands' siblings and children. Five of the cases observed were from the generation of the probands' grandchildren, and few of their parents have passed much of the risk period for Alzheimer's disease. Hence, too, no meaningful risk estimate for Alzheimer's disease in children of probands can be made. Myeloproliferative disorders: the age-corrected expectations were computed from the *Third National Cancer Survey: Incidence Data* [*Natl. Cancer Inst. Monogr. No. 41* (1975), table 20B]. Incidences of leukemia, lymphoma, and multiple myeloma were summed to arrive at total.
15. I thank V. E. Anderson and I. I. Gottesman for their comments. A. Mastri was a consultant in neuropathology and did most of the neuropathologic examinations. The late R. Rossen established the neuropathology laboratory and thus made the work possible. J. White did many of the field interviews. Financial support was provided by grant MH2458801, Center for Epidemiologic Studies, HEW, and the Phillips Foundation.

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