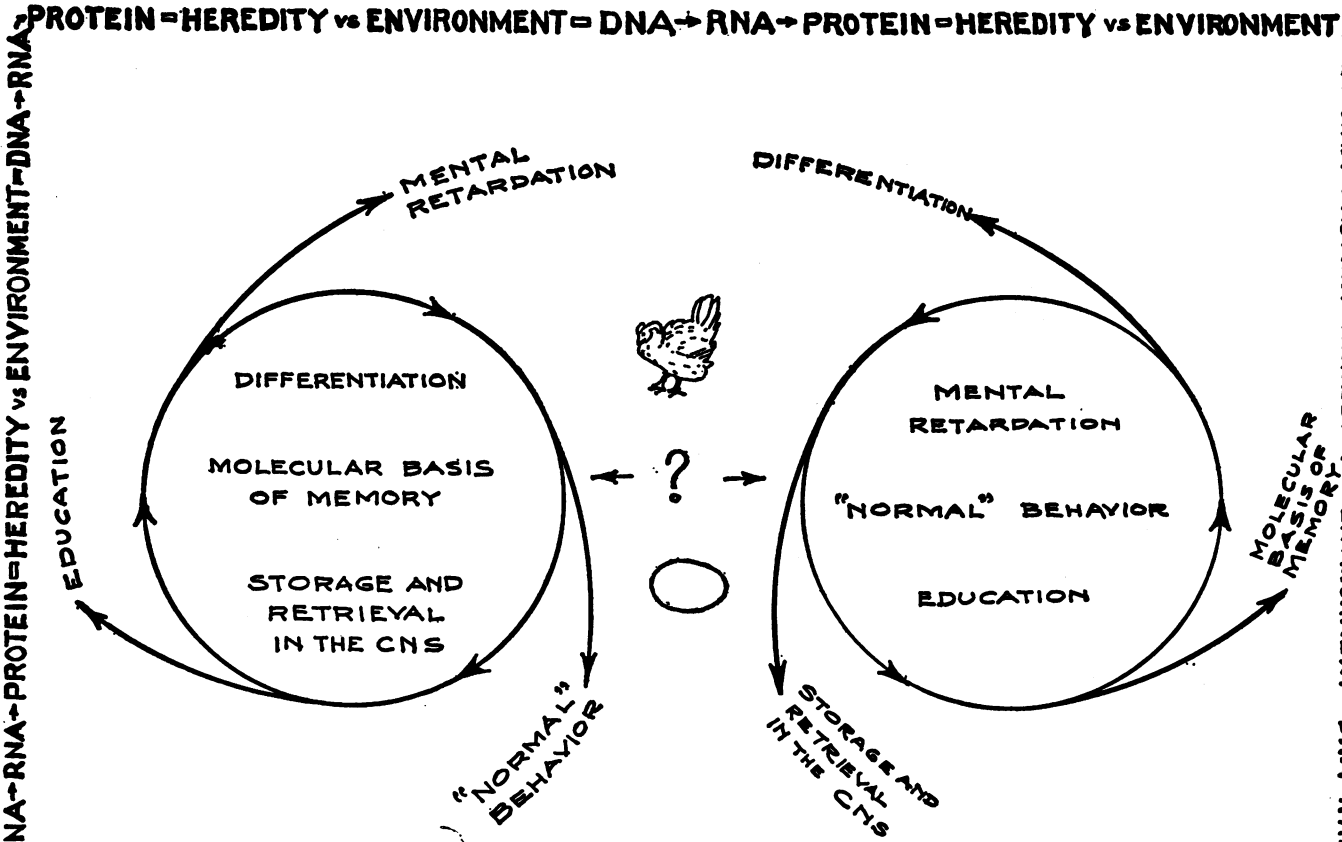

Molecular Approaches to the Central Nervous System

AAAS Symposium • 29–31 December 1968 • Dallas, Texas

"This patient illustrates another aspect of the syndrome—he had to be kept with the hands securely tied to prevent destructive biting of the fingers. This behavioral characteristic of the syndrome may well be the most striking aspect of the clinical picture. At first thought one might think that this was a manifestation of some type of sensory anesthesia, but this is not the case. These children have a compulsive behavior. —This extreme degree of self-destructive activity about the face was progressive. He looked at first like a patient with a congenital hairlip and cleft palate. However, when he was born, his lip and palate were completely intact. —These children are generally aggressive and self-destructive. —Aggression against the outside world is very direct, expressing itself in blasphemous language with intense swearing, putting parents in embarrassing situations. Two boys developed the disturbing habit of pinching the mother's breasts when she was holding them, and subsequently, pinching the genitalia of the father. They did these things any time, any day, or place. One cannot underestimate the overall aggressiveness of these children. —Older children do not generally bite others. They hit or kick, knock glasses off, and laugh uproariously. The younger ones bite first. Most parents of affected children have been bitten. There are some fairly dramatic examples. Nurses in the clinical research unit must learn to avoid or adjust to this type of behavior. It takes a certain maturity to manage a boy who pinches. —Mental retardation is rather difficult to assess in the presence of choreoathetosis. We are impressed that these children do not seem to miss much that goes on about them. One patient, when asked why he bit his finger replied with a glint in his eye, 'My uric acid's too high.' —It has been most impressive in view of their appearance, limitations, and behavior to find them unusually engaging children and often particular favorites of the nurses and other members of the hospital staff."

The above statements were taken from a series of seminars on the Lesch-Nyhan Syndrome [*Federation Proceedings* **27**, 4 (July–August 1968)]. It was also pointed out that it was important to identify clinical features of the syndrome since careful assessment of clinical similarities and differences may elucidate much heterogeneity. "Four clinical characteristics appear clearly to be parts of the syndrome, that is, mental retardation, neurological abnormalities (choreoathetosis or athetoid cerebral palsy), obsessive destructive behavior, and hyperuricemia (certain features of clinical gout)." Hyperuricemia itself is not constant, but increased secretion of uric acid is. The most constant manifestation is the aberration of purine synthesiss. In a 4-year period researchers collected information on over 60 patients and studied 15 in detail. Therefore, a relatively common metabolic disease is a distinct

cause of mental deficiency. "*It also appears to be the first condition to be recognized in which characteristic biochemical abnormalities are associated with a reproducible pattern of abnormal behavior.*" The characteristic biochemical abnormality has now been defined [*Science* **155**, 1682 (1967)] as the complete absence of an enzyme, hypoxanthine-guanine phosphoribosyltransferase, HG-PRTase, which catalyzes the following reaction.

$$\text{PRPP} + \text{hypoxanthine or guanine} \rightarrow \text{IMP or GMP} + \text{PP}$$

Previously this enzyme was accepted as a component of the salvage pathway for purine metabolism with no hint of a relationship to the control of de novo purine synthesis. The complete absence of the enzyme is apparently associated with the neurological changes in the Lesch-Nyhan syndrome and other examples of excessive purine synthesis (gout) are also associated with greatly reduced levels of enzyme activity. Apparently, a low level of activity has an ameliorating influence on the neurological aspects of the disease.

A symposium entitled "Molecular Approaches to the Central Nervous System" was developed 29–31 December 1968 in Dallas, Texas. The symposium was developed as a sequel to the 1967 symposium which will be forthcoming in book form through Academic Press under last year's symposium title, "Molecular Approaches to Learning and Memory." The previous program emphasized [*Science* **158**, 1081 (1968)] experimental approaches which could lead to an understanding of the nervous system at the molecular level. Some of these same subjects are represented in the 1968 symposium, but the session entitled "Molecular Approaches to Mental Retardation," chaired by Robert E. Cooke, has been selected to emphasize those areas in which human biology (pathology) and molecular understanding go together. The first two speakers, Marcus Jacobson and Merril K. Wolf, represent selective ("editorial") emphasis to the end that development of the nervous system is an important and fertile area, but the remaining presentations represent paired-presentation on a single subject which will cover the full spectrum from the clinical syndrome to the chemical evidence.

The preview of the Lesch-Nyhan Syndrome was given to illustrate a possible paired presentation. It also seems possible that the association of a reproducible pattern of abnormal behavior with aberrant purine metabolism and the identification of an HG-PRTase deficiency with the metabolic defect represent contributions which should be compared to the sequential understanding of the hemoglobinopathies based on the contributions of Linus Pauling, Harvey Itano, and Frederick Sanger which had subsequent far-reaching consequences for molecular biology and genetics. A prediction of the progress which can be anticipated in the next 10 years (including the influence of the Lesch-Nyhan Syndrome) would be difficult to make and undoubtedly would meet with a controversial response, but the chairman and speakers in the symposium represent a sample of those who have committed themselves to an understanding of the central nervous system with the implied assumption that the current concepts of molecular biology (Stent's central dogma) will be applicable. An ultimate understanding may require the development of an avant-garde attracted by "the hope that some 'other laws of physics' may yet turn up through the study of the nervous system" [G. S. Stent, *Science* **160**, 390 (1968)], but in the meantime some progress can be anticipated by efforts which are interdisciplinary to the point where basic versus applied and clinical versus preclinical have no meaning.

A specific historical evaluation at some future date may imply that progress was made as a result of spin off from a discipline-oriented approach. It also seems possible that the interdisciplinary approach would lead to a historical evaluation which would have to include: (i) An age old question . . . which came first . . . ? . . . and (ii) A space-age question . . . who spun off what to whom?

WILLIAM L. BYRNE
College of Basic Medical Sciences, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tennessee 38103

Molecular Approaches to Central Nervous System (29 Dec).

Chairman: William L. Byrne.
Historical Review of Memory Transfer, Ejnar J. Fjerdingstad.
Memory Transfer—Specificity and Reproducibility, Georges Ungar.

Molecular Approaches to Mental Retardation (30 Dec.)

Chairman: Robert E. Cooke.
Introductory Remarks.
Prewiring of Nervous System, Marcus Jacobson.
Organotypic Culture Analysis of Disease Mechanisms in Neurological Mutant Mice, Merril K. Wolf.
Mental Retardation and Nutrition: Clinical and Biochemical Aspects, P. Dodge and D. Cheek.
Clinical, Behavioral, and Biochemical Aspects of the Lesch-Nyhan Syndrome, William L. Nyhan and J. Edwin Seegmiller.
Inborn Errors of Complex Lipid Metabolism: Clinical and Biochemical Aspects, Roscoe D. Brady and Guy M. McKhann.
Mucopolysaccharidoses: Clinical and Biochemical Manifestations, Andrew E. Lorincz and Elizabeth Neufeld.
Behavioral and Biochemical Aspects of Trisomy, George Smith and R. Rodney Howell.

Molecular Approaches to Learning and Memory (31 Dec.)

Chairman: Henry P. Mahler.
Detection of Unique RNA Species by Hybridization Procedures, John Gaito.
The Effect of Short Term Training on RNA Polysomes, Edward Glassman.
Current Studies of Memory Formation in the Goldfish, Bernard Agranoff.
Hippocampal Function in Memory, Peter Carlton.
Pigeon Brain Mucoids and Training, Learning and Memory, Samuel Bogoch.

Molecular Approaches to the Central Nervous System

William L. Byrne

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