

## MEMORANDUM - Research on Mental Retardation

Notes by Joshua Lederberg, Stanford University

1. Requirements for and limitations of basic research bearing on mental retardation -

It is difficult to see how we can make outstanding progress in mental retardation and cerebral disfunction without some better understanding of the mechanisms of normal cerebral function, particularly learning. After many years the biology of intellect remains a deep mystery and there is no consensus as to the soundest approach, although exciting results certainly continue to appear from electrophysiological studies.

Under the pressure of urgent need for the solutions to human problems it is easy to misconstrue the possibilities of basic research in supplying the information needed for the solution of such problems and there is always an understandable tendency to push research that seems to be most immediately related to the critical disease situation. If carried too far, this may be a misguided, even harmful bias. Many of the most outstanding advances in our comprehension of the complex problems of mental retardation have come from entirely unrelated fields. For example, the brilliant new insight that has been achieved in the ideology of mongolism stems directly from the most general investigations of the chromosome number in man which in turn has its bases in the studies of chromosome variation in the formation of species and varieties in domestic plants. Our present techniques for the accurate diagnosis of galactosemia depend on basic studies on the metabolism of sugars by yeast which could not have been directly motivated by concern for mental retardation. These examples could be multiplied many fold. Are we then helpless in attempting to accelerate the development and application of basic research information through the problems of mental retardation? A constructive answer is possible and has two elements:

1. To provide continued encouragement for the opportunities for basic research in a variety of fields with special emphasis on the provision of adequate facilities to insure the most efficient use of existing technical manpower in the development of scientific information and

2. Disseminating information on and a more acute interest in the more immediate problems of mental retardation among such scientists. If we on the panel do our jobs well, it will be these scientists and not we who will discover the salient opportunities.

It should be stressed that the resource of creative scientific talent is not an unlimited one. Much still remains to be done in providing adequate educational opportunities, especially at the earlier stages of academic training, to insure the most effective development of career opportunities for creative talents. At the present time the most effective scientific talent is spread very thin and has many demands for the development of basic knowledge and for the application of this to applied problems in many fields of human endeavor.

Probably the most effective course that can be adopted for the immediate future is to provide adequate facilities so that this talent can have its most efficient application to meet the social demands upon it. An indiscriminate distribution of research funds could have the opposite effect, of attracting into new research areas an ever more marginal range of personnel with what may be indifferent and even negative consequences for the total output of creative scientific work. The same result is likely to be achieved if an unbalanced program that does not give adequate attention to the free range of research inquiry is overstressed.

2. In a few cases we can hope to achieve some insight into ideology and nosology of mental retardation without fully understanding the terminal mechanisms. For example, the chromosome nondisjunction in mongolism; a homozygous recessive gene in phenylketonuria or galactosemia. By differentiating specific diseases within the complex of mental retardation we can at least focus on some more specific problems and begin to ask pertinent questions.

In critical research then we should place strong emphasis on explicit characterizations of the defects among different cases of mental retardation. For example, some children may be worried to death of the word blind due to central failures - in an ordinary educational regime they may be found to be ~~un~~ "unteachable". The further development of analytical techniques may help to analyze other defect patterns in a more meaningful way so that we have some starting point for research as well as diagnosis and therapy. Needless to say, such studies have important implications for the differentiation of pedagogical technique among normal as well as diseased children. We have to educate ourselves and our audience to stop thinking of mental retardation as a fundamentally unified disease, an approach which can only obscure the analysis of the specific defects which operate in different examples of it.

The development of sophisticated analytical technique, behavioral, neurological, biochemical, is also essential for the earlier diagnosis of mental retardation. So little is known about the details of delivery and immediate postnatal experience among normal children that it is difficult to evaluate the role of marginal traumatic injury, cerebral ischemia, delayed respiration and inoxia, virus infection, and so forth, in a large segment of diseases attributable to perinatal accidents.

3. The bearing of research in a) molecular biology and biophysics, b) cell biology, c) genetics.

a) The electrophysiology of the nervous system remains a highly promising area of investigation, especially with the growing application of computer methods to the analysis of output data. This field in relation to the whole area of biomedical electronics and instrumentation needs more financial support - it is inherently very costly and this has discouraged many investigators from the ambitious planning needed for innovations here.

The chemistry of the nervous system is in a discouragingly primitive state. It is impossible to frame significant questions about deviations in development when we cannot properly describe the variety of proteins and other specific compounds in the intact adult normal brain. If we only had this framework we could then begin to dig into the bases of cellular specificity, metabolic interaction, developmental patterns and their variation with genetic factors and environmental disease. At the present time it is as if we were trying to cope with the anemias as a clinical problem while lacking any knowledge of the chemistry and physiology of hemoglobin.

b) Morphological and functional investigations have talked a great deal about the organization of the central nervous system, but we still have only the most primitive understanding of the functional relationships of different cell groups in the brain, and more particularly, the developmental mechanisms by which these are brought into effective working relationship with one another. Such studies of developmental neurology as are typified by Sperry's work of some years ago should be expected to give us a tremendous insight into the biology of neural patterning. Unfortunately, these studies were stymied in midpath for lack of the chemical insight alluded to in the previous section. More recently, related question of specific functional biochemical relationships of cells have appeared, for example, in Morrell's studies of functional changes induced by epileptiform discharge - once again, these are blocked by the virtual nonexistence of a science of molecular biology of the nervous system.

We are at a similar impasse in our attempts to understand the mechanism of cellular intoxication in two diseases for which we have some biochemical insight, galactosemia and phenylketonuria.

c) Genetics - Studies of human population genetics of a rather general kind, especially the effects of consanguinity such as are going on in Hawaii, Northern Italy, Japan, and elsewhere can be expected to throw tremendous light on the role of genetic factors in mental retardation. From such a general approach, we may hope to be able to analyze specific syndromes attributable to particular genes having individualized by chemical effects.

Mongolism represents one of the most formidable problems in this area and the recent discovery that this is based on chromosome nondisjunction and the production of viable individuals carrying an extra chromosome has given us a tremendous lead in this field. However, a great deal remains to be done 1) in the understanding of the cell biological mechanism of the chromosome aberration - why it happens in the first place in the developing egg, and what bearing maternal age has on the cytological process and 2) the identification of other genetic factors located on this extra chromosome that may give a better understanding of the way in which the development of the child is influenced by it. It is quite likely that many other syndromes based on chromosome aberration

are now included in the waste basket of mental retardation of unknown <sup>eti</sup>iology and these should yield to more extensive cytological investigation.

## Additional Note -

As a laboratory scientist, I can point to some of the most urgent difficulties that we face in endeavoring to expand our basic research programs so that they can take proper account of the challenges posed by problems such as mental retardation. Over the years, the National Institutes of Health program of research grants and research training grants have developed splendidly, and their present level and rate of growth promises very well for the availability of essential resources in such research. However, for reasons that are entirely inexplicable to me, the pattern of nongovernmental support suffers from a serious distortion in the curious unwillingness of many donors to furnish funds for the one aspect of research expansion that is most difficult to develop from other sources: the physical facilities in which people can work, BRICKS AND MORTAR. The availability of federal funds for operational costs of research programs in medical science and the constructive evolution of the techniques for program review and evaluation within the NIH can give us a splendid national program which hardly needs to be duplicated by nongovernmental agencies. However, Congress has been reluctant to face the urgent needs for more research facilities - the past and existing programs under the health research facilities acts being grossly inadequate. This is the area in which private donors should concentrate their activity in order to make the most effective use of available funds, since these will be amplified many times in the operating funds which effective research workers can obtain for the manning of such facilities.

Memorandum to Dr. Davens

This note is outside the research question, but surely it must have occurred to many people that we need more adequate provision for insurance to mitigate the financial burdens of special care for such congenital diseases as mongolism. The penalties to the family and siblings in incidents of this kind are severe enough that we should have some better means than we now do of preventing the impact of the additional, sometimes very serious, economic burdens. It seems questionable whether the Congress is yet ready to incorporate such a program into the general social welfare system. But perhaps here, more than in other areas of family security, a great deal could be done to start with even by a strictly private voluntary insurance program. Apart from its obvious social benefits, such a program could also generate a very useful research tool by defining a well characterized and well examined population in which the incidence of mental retardation and its variety was under the most careful, uniform study.

cc: Dr. Leonard Mayo  
Mrs. R. Sargent Shriver, Jr.