OFFICE MEMORANDUM • STANFORD UNIVERSITY

draft by DL

DATE: April 5, 1960

TO :

FROM :

SUBJECT: **PROGRAM IN MOLECULAR MEDICINE AND NEUROBIOLOGY**

Proposal to Kennedy Foundation from N. Kretchmer, M.D., Professor of Pediatrics, J. Lederberg, Ph.D., Professor of Genetics, K.H. Pribram, M.D., Associate Professor of Psychiatry.

Stanford Medical School, among similar institutions throughout the country, has a particularly strong orientation towards fundamental scientific research in an academic context. The suburban community, though offering plentiful clinical challenges in teaching material, does not present the huge burden of clinical responsibilities found in urban centers; the recent move to the University campus has underlined the opportunity to develop medical research in education along academic lines and this aim is not diverted by the pressures that bear on state-supported schools. The full realization of these opportunities and the most fruitful cultivation of the existing staff urgently requires a great deal of financial help for further building, for salaries for new staff, for operating expenses in support of the wide-range research activities that bespeak an active and well-rounded community.

We are offering this digest of our own personal and departmental programs in the belief that some elements at least will relate to the objectives of the Kennedy Foundation and justify its support. The amounts we are requesting will be, and in any case would have to be, matched by funds from other sources to support the entirety. Although we have found some common bond of interest in discussing these problems with one another, we have found it difficult to describe this in compact, easily understood terms. "Molecular medicine" should convey the application to medicine and further fundamental work in the field of "molecular biology" -- biochemistry, biophysics, genetics, and cell biology. "Neurobiology" should be thought of in the same context with special stress on the translation of neural mechanisms into overt behavior.

We would not wish to offer fanciful exaggerations of the imagined "interactions" of these fields. We are each responsible investigators with well-directed programs and must consult our own judgment as to the fruitfulness of each item we may wish to pursue. In the last analysis it is these programs we need support for and our claim for this is based on our individual qualifications and past performance. But we have already found a number of points on which we could offer our own unique insights and the close physical proximity of these research units is bound to encourage this kind of "interaction" as a possible bonus to the individual programs. The Pediatrics group plays a central role: its concern with developmental biochemistry and with clinical genetics overlaps extensively with the activities in genetics and in developmental physiology and performance of children, with those of neurobiology. But even Lederberg and Pribram talk to one another too. As pointed out earlier we are planning to organize a joint seminar as one way of focusing attention on problems of mental retardation, not only to sharpen our own thinking, but that of our colleagues, house officers and students

throughout the school.

SPECIFIC RESEARCH PROGRAMS

1. Here we will each put our own appendices perhaps it would be appropriate to have, say, a one half page summary of each of them and leave the fuller texts like those that both of you have submitted for appendices to be headed on later on.

MATERIAL REQUIREMENTS (Budget)

1. This is again something we have to work out.

Your committee may well be entitled to ask what claim should this program make on the Kennedy Foundation with its particular dedication to problems of mental retardation? We have pondered over this ourselves and believe your interest can be justified in the following terms despite the fact that most of our efforts would not be directed to the study of mentally retarded children as such. We certainly lack no sensitivity to the importance of the problem of mental retardation be it in social, clinical, or scientific terms. In formulating an attack on this problem, certainly one avenue is topical study with a specific disease orientation concentrated on patients suffering from retardation. We can readily applaud the support which the Foundation has given to Centers elsewhere for work along these lines. It is obvious, however, that we lack a considerable body of fundamental scientific information on areas which may be seemingly remote from the problems of retardation; if this were not so, concrete programs for coping with this problem on the basis of existing knowledge would be evident. We therefore believe that a foundation, such as the Kennedy Foundation, should recognize its responsibility to support long-term, basic research to complement disease-oriented projects so as to generate a balanced over-all program.

Mental retardation has obvious roots in human genetics, biochemistry, development, and the neural mechanisms which underlie effective behaviour. From this standpoint, it would take superhuman perception to define those areas of scientific study within these disciplines which could be excluded as capable of making potential contributions to the solution of the problems of mental retardation. Again, if we had such insight, the practical measures we should have to adopt would be far more apparent than they are today. It would be easy to contrive more or less valid extrapolations to illustrate how particular lines of experimental work conceivably might bear directly on mental retardation. However, we would not wish the Committee for the Kennedy Foundation to be unduly impressed with our ingenuity in this respect and would prefer that they give the greatest weight to the general scientific validity of our program. However, it may help to illustrate the principle of the connection between seemingly unrelated lines of scientific investigation with a few examples.

1. During the past year ~~year~~ our understanding of one of the major categories of mental retardation, Mongolism, has been greatly advanced by the discovery that this syndrome is associated with the presence of one extra chromosome in the nucleus of each cell of the developing individual. This chromosome unbalance must result from an abnormal cell division in the developing egg which results in a so-called "non-disjunction" of a separating chromosome pair. In consequence one cell receives an extra chromosome whose

normal destiny would have been to be part of the normal make up of the other daughter cell. The effect of maternal age on the incidence of Mongolism suggests that environmental factors play a major role in the occurrence of nondisjunction but we have not significant knowledge of what these environmental factors are. In addition, there are indications that some families show a genetic predisposition to the occurrence of this nondisjunction. It happens that for several years, the role of nondisjunction in bacterial genetics has been a major aspect of Lederberg's research program. Some time ago a specific gene, originating by mutation was discovered to greatly increase the frequency with which nondisjunction occurs in bacterial matings. In addition the variability in the frequency of chromosome nondisjunction from experiment to experiment shows that some environmental factors not yet well-defined are important in the production of this anomaly. In addition, the unbalanced chromosome types which result from bacterial nondisjunction furnish an important tool for the study of chromosome interactions; conversely the bacterial system gives us excellent experimental material for understanding how chromosome unbalance can influence the performance of a cell and this in turn would give us further understanding of why the additional chromosome results in the abnormal phenotype in the case of Mongolism. Further, much of the work in genetic analysis of enzyme formation in Lederberg's laboratory has concerned a series of mutations which affect the metabolism of the sugar galactose. One class of these bacterial mutants is deficient in the enzyme uridine-diphospho-galactose-transferase. It happens that a precisely analogous metabolic defect is responsible for the condition congenital galactosemia in man which is, fortunately, a relatively rare sort of mental retardation in children. Other metabolic anomalies, for example phenylpyruvic oligophrenia, also have their biochemical genetic counterparts in bacterial mutants. We do not know how these defects in specific metabolic steps result in the damage to the nervous system which characterizes children suffering from these diseases. Research is continuing at the present time, however, on the mechanism of toxicity to bacteria of the metabolic intermediates which accumulate in cultures of these mutant organisms in consequence of these metabolic blocks. Kalckar, using some of the Lederbergs' cultures has already adduced evidence that galactose-1-phosphate, accumulating in "galactosemic" bacteria is toxic to them and that it may be the immediate culprit in the developmental defect in galactosemic children. These examples from bacterial genetics are perhaps the most remote in their potential relationship to mental retardation. However, they deal with the most general issues of the control of genic activity which must underline not only biochemical but neurological and behavioral development. More explicit examples of gene-controlled effects on enzymes, and the enzymatic components of normal development, are the preoccupation of several members of the Department of Pediatrics.