For those of you who are interested in the subject, I should like to refer you to an article appearing in the May, 1959 issue of the American Journal of Mental Deficiency which contains an article titled, "A Survey of Research in Institutions for the Mentally Retarded". This was made by Harvey A. Stevens, now Superintendent of Central Wisconsin Colony and Training School, Madison, Wisconsin, while Superintendent of the Edward R. Johnstone Training and Research Center, Bordentown, New Jersey, and two associates. Questionnaires had been sent to superintendents of 90 state owned and superintendents of 5 privately owned institutions for mental defectives having a resident population of 300 or more. Returns were received from 42 state and 5 privately owned institutions and represent 49.5% of institutional sample that received questionnaires and 100% of the privately owned.

The mental classification of the combined resident population of these institutions which had a total population of 73,756 included 5.9% borderline (I.Q. 76 plus); 22.3% mildly retarded (I.Q. 50-75); 44% moderately retarded (I.Q. 25-49); and 27.8% severely retarded (I.Q. 24 minus). Mr. Stevens found that "it would be difficult to classify more than some nine institutions or 19% of our sample as possessing this type of research program, (a coordinated long-range effort of personnel who devote at least 50% of their time to the systematic collection, analysis and reporting of data)". The reasons given for the absence of research by those institutions who comprise the "no research" category, most frequently mentioned (80%) is the fact that "the professional staff is too occupied performing service functions to have time for research". Tied for second and third place mention respectively "are a lack of funds" and the "inability to recruit trained research personnel" (60%). He observed that it was encouraging to note that a "lack of interest at the institu-
One of the most striking findings of his survey was the clear cut awareness of the importance of research that exists in the institutions for the retarded. Moreover, the 215 studies reported by the participating institutions indicates that this awareness is more than academic.

He found that approximately 83% of all research reported is in the fields of medicine and psychology, medicine contributing 46% and psychology 37%. The remaining 17% falls into the category of education (10%), sociology (5%), and administration (2%). A more specific delineation of areas within research categories indicates a relatively heavy concentration of medical research in the sub-areas of (a) bio-chemistry (36%), (b) medical surveys (31%), (c) psychopharmacology (tranquilizers) (15%). A similar breakdown within the psychological classification reveals concentrations in the following areas: (a) Personality-adjustment (28%), (b) Human learning (18%), (c) Perception (15%), (d) Tests and measurements (12%).

In view of the rather substantial research contributions being made by the institutions participating in this survey, it was eye-opening, indeed, to learn that approximately 80% of these institutions received no monies allocated for research from their institutional budgets for the fiscal years 1956-57 and 1957-58. In fiscal 1956-57, a total of $167,808 was allocated for research from the institutional budgets of all participants. This figure represents approximately one-fifth of 1 per cent of the total budgets of these institutions. In other words, in fiscal 1956-57 less than one-fifth of a penny from each institutional dollar was earmarked for research. In fiscal 1957-58, this figure is even lower ($110,195), approximately one-eighth of a penny from each institutional dollar going for research.

Mr. Stevens found that approximately two and one-half times as much money as was allocated from institutional budgets for research in fiscal 1956-57 was obtained from non-institutional sources ($385,284). These monies were obtained by fifteen of the institutions participating in the study.

For fiscal 1957-58, $515,465 was obtained by thirteen institutions from non-
institutional sources. This figure represents approximately five times the total amount of all institutional allocations for research for this same period. If it is permissible to talk of a trend based on research allocations for only two consecutive years, it would seem that non-institutional support for research is increasing, whereas institutional support is decreasing. Although the total of institutional funds allocated for research in 1957-58 is only some $50,000 less than in fiscal 1956-57, total budgets have almost uniformly increased for this period so that the percentage of monies set aside for research has decreased more sharply than this $50,000 figure might indicate.

If total research funds are compared, these data indicate an overall 13 percent rise in funds available for research in fiscal 1957-58 ($625,660) as compared with fiscal 1956-57 ($553,092). That this increase is probably insufficient is mirrored by the fact that approximately 55 percent of those institutions doing research indicate that their single most salient problem derives from the continuing need to obtain funds to subsidize their research programs.

It seems clear that strong research interests exist in the institutions for the retarded. It also seems fair to conclude that at present this disposition toward research has far outstripped the availability of funds. Non-institutional financial support for research appears to be increasing, whereas institutional support seems to be decreasing.

More than 500 persons from 28 states, Canada and South America attended a three-day conference on "Approaches to Research in Mental Retardation" held May 1-3 in Philadelphia. I had the good fortune of attending the first session which occurred on the evening of the last day of the annual meeting of the American Psychiatric Association.

Twenty major research centers were represented in the roster of participants for the conference which was co-sponsored by the Technical Planning Project of the AAMD and the Woods Schools for Exceptional Children, Langhorne, Pennsylvania.

Dr. Nicholas Hobbs, Chairman, Division of Human Development and Guidance, George Peabody College, Nashville, in his address to the first session of the
conference said, "I think we can well be sanguine today about the prospects of achieving greater control of mental retardation through greater understanding of the processes pertinent to it from the biological to the sociological level."

However, he warned that, "Research in mental retardation has been hobbled by the tendency to conceptualize the problem in unitary terms. New conceptual differentiations should not only make research on mental retardation more attractive to new talent by making it more plausible, but also make clear the potential significance of mental retardation for many kinds of research in which its relevance is seldom recognized."

At the same time, Dr. Hobbs urged a continuing "Frontal assault" on the problem by scientists working on some specific problem in the field of mental retardation.

In looking toward the future, Dr. Hobbs said, "Research programming in the field of mental retardation should be guided by concerns for the cumulative effects anticipated as a result of any particular research investment."

In describing the peculiar administrative aspects of research, he advised, "The administration of research requires a different set of guiding principles from those that have proven effective in other management situations. In fact, few things can inhibit research more drastically than 'efficient administration' in the customary sense."

Dr. Thomas Gladwin of the National Institute of Mental Health, reported, "Intelligence tests, which are essentially limited to measuring school ability, cannot satisfactorily predict how an individual will fare once he leaves school."

Speaking on a panel program, Dr. Gladwin pointed out, "Many adults considered definitely retarded when they were in school 10 or 20 years ago are now leading pretty normal and useful lives."

Dr. Richard I. Masland, National Institute of Neurological Diseases and Blindness, speaking on the same panel, said that in mental subnormality we are not dealing with a disease but with a symptom which may be the result of any one of a number of diseases. He urged the importance of keeping detailed prenatal and obstetrical record
Complications in pregnancy and prematurity can come from lack of protein in the mother's diet, Dr. Benjamin Pasamanick, Ohio State University, stated in his discussion of organic factors involved in retardation. Research teams, investigating dietary inadequacies, could make invaluable contributions to current information in this field, he said.

Dr. Theodore Greiner, Baylor University Medical School, Texas, predicted: "Swarms of new drugs, in the years just ahead, will be advocated for patients. The administration of these drugs changes the doctor's psychological tone as surely as it does the patient's—and both of these factors must be considered."

"We Americans believe there is something wrong with research which doesn't produce a cure," said Dr. Margaret Mead in her address to the conference. Dr. Mead is the associate curator of Ethnology, American Museum of Natural History, New York.

She charged that research in the field of mental retardation is exceedingly threatening to our present structure of educational research and medical diagnosis, adding, "Perhaps the greatest contribution which research in this field can make, is to cause us to question and question again the narrowness of our school system, the meagerness of our conception of education, the provincialism and inadequacy of our intelligence tests, the restricted character of our conception of humanity, the poverty of our ideas about individual differences, and our unwillingness to investigate anything unless we can somehow change it."

Proceedings of the conference as well as the papers presented will be published in September as a special issue of the American Journal of Mental Deficiency.

Reports show that $330,000,000 was spent for medical research alone in the United States in the year 1957. This came from the following sources: philanthropy, 16%; endowment, 6%; government, 57%; industry, 21%. It was utilized in university and medical school laboratories, 50%; government laboratories, 23%; and in industrial laboratories, 27%. A conservative estimate of national medical research expenditures is that they will reach $900 million to $1 billion per year by 1970. The paramount problem not only in medical research but in every field of research activities is
the critical shortage of scientific personnel. There are more people engaged in medical research today than ever before, but the competition for qualified personnel in this area constantly increases. It is estimated that an additional 6,000 M.D.'s and/or Ph.D.'s will be needed by 1970 if the nation's medical research program approximates the 1970 estimates.

The critical situation that exists for available qualified research workers is indicated by the Statement of Principle of the Pharmaceutical Manufacturers Association commended by the Board of Trustees of the American Medical Association as reported in the August 10, 1959 issue of the AMA News from which the following quotations are made:

"PMA said that in the allocation of federal funds for medical research, these principles should be followed:

The training of additional teachers and research personnel should have highest priority since further progress in medicine directly depends upon the supply of highly qualified scientists.

Government funds should be principally allocated to basic research objectives, to expand fundamental knowledge in all medical fields, rather than to applied research and development.

Except in unusual circumstances, government funds should be allocated to non-profit institutions, such as medical schools, hospitals and research institutions, rather than to private industry. Private industry should be subsidized in cases where no non-profit organization can do the job.

PMA pointed out that government subsidies for industrial research would accentuate the manpower problem facing medical research."

The public must realize that those engaged in medical research are highly trained personnel who have spent long periods in becoming prepared and require adequate physical facilities where research is to be done,

The New York Times of April 8, 1959, printed the details of a news conference with Secretary, Arthur S. Fleming, of the Department of Health, Education and Welfare,
on the subject of a new study to determine cerebral palsy and mental retardation in children. Mr. Fleming stated that no such study has ever been made in the field of neurological illness and that the Public Health Service is undertaking a five year study of 40,000 pregnant women in an effort to find the cause of cerebral palsy, mental retardation and other birth injuries.

Mr. Fleming estimated that 1,000 mothers would be studied the first and more than 8,000 each of the next four.

A study design has been developed so that all data on birth will be collected and recorded by the Public Health Service in cooperation with sixteen hospitals.

In each cooperating hospital, Mr. Fleming said, data will be collected by geneticists, epidemiologists, psychiatrists, psychologists, sociologists, obstetricians, physiologists, pediatricians and neurologists. The study is being confined to hospitals having strong staffs of such specialists.

The cooperating hospitals are: Boston Lying-in and Children's Medical Center; Brown University, Providence; Charity, New Orleans; Philadelphia and Children's; Children San Francisco; Columbia Presbyterian Medical Center and New York Medical College; Johns Hopkins, Baltimore; Medical Center of Virginia, Richmond; University of Minnesota, Minneapolis; University of Oregon, Portland; Yale University School of Medicine, New Haven; University of Buffalo; and University of Tennessee, Memphis.

You will be interested to learn that at present there are two special projects in progress here—the one is a true research project which I shall mention later, the other is participation in a Minnesota Cerebral Palsy Study which is being conducted by Helen M. Wallace, M.D., Professor of Maternal and Child Health, School of Public Health of the University of Minnesota. The co-sponsors are the University of Minnesota School of Public Health, United Cerebral Palsy of Minnesota, Minnesota State Department of Health, Minnesota State Department of Education and Minnesota State Department of Public Welfare. This study is described by Dr. Wallace as one "of the needs of people with cerebral palsy in the State of Minnesota. This project has been approved by the Minnesota State Medical Society. The purpose of this study is to
determine the services which patients with cerebral palsy are already receiving, and the necessary services not now provided." We are preparing the information requested in regard to over 400 of our cerebral palsy patients who are mentally retarded. Dr. Thorsten Smith, our Director of Medical Services, is in charge of the staff completing these questionnaires each of which requires an average of over two hours of time.

The special research project in which we are engaged is one being conducted under the immediate supervision of our Pediatrician and Director of Laboratories, Dr. Heinz Bruhl. He is assisted by our consultant in internal medicine, Dr. J. Arneson, and by Mr. Martin Bruhl, chemical consultant. The biochemical procedures necessary in this research were established by Martin Bruhl in cooperation with the University of Minnesota and are carried on by a full-time laboratory technician.

When this program was first planned he agreed to discuss this project with you today. However, he is on vacation in Europe but submitted a written report which I shall read, following which there may be a discussion of research going on in the field of mental retardation. His report is as follows:

"In our total population of about 3,300 patients, we have identified 32 cases of a specific type of mental deficiency which usually is severe and diagnosed as 'phenylpyruvic oligophrenia' (Phenylketonuria, P.K.U.).

The diagnosis is made by a simple chemical test of the urine, which we have done routinely since 1945: 5% Ferric Chloride in acidified urine produces a blue green color. A recently developed diaper test and paperstrip test (Phenistix) make it possible to perform urine tests even on uncooperative patients. In a recent survey of our entire population we used the Phenistix method to our full satisfaction and found 11 additional cases (9 definite, 2 doubtful ones) which are not included in this survey.

Physical Characteristics:

Many of these patients are light blond, have blue eyes and a fair skin, and are mostly of Scandinavian or German stock. 11 of our patients are moderately
retarded (trainable level), 21 are severely retarded (custodial level). 21 have signs of cerebral palsy of varying degree, 9 are subject to convulsive seizures. 16 have a tendency to eczema, dermatitis and furunculosis. 7 of our patients are under 10 years of age, 10 are teen-agers, the other patients are 20 years and older, 3 of them between 50 and 60, and 2 even above 60. Both sexes are equally distributed in the group.

Metabolic Error:

This mental condition is connected with a metabolic error. Due to the lack of a certain liver enzyme, 'phenylalanine-hydroxylase', these patients are unable to oxidize phenylalanine, an amino-acid which is normally present in our daily food and essential for the formation of tissue protein. This amino-acid accumulates in brain and tissues, and rises to abnormally high levels in the blood of these patients. It is excreted in the urine as phenylpyruvic acid. It is the presence of this metabolite which has given the name to this type of mental deficiency.

Recent studies (1953—59) in England, Germany and U.S.A. have shown that a phenylalanine-free or restricted diet will correct the metabolic error in these patients and reduce the high phenylalanine levels in their blood. When diagnosed early and placed on such a special diet within the first 2 years of life, most of these children have improved in their behavior and intelligence and show more or less normal development. Dr. H. Berendes and Dr. John Anderson, University of Minnesota, have a group of 7 patients who were diagnosed as phenylpyruvics during the first 2 or 3 months of life and who were then placed on the restricted diet. Thus far these children are developing normally, physically and mentally, instead of becoming mentally retarded.

As the studies at the University are carried on with young children and ours with older patients, they complement each other.

Research Grant:

In April, 1957, we received the first State Research Grant for establishing our biochemical laboratory through Dr. Dale Cameron, Director of Medical Services, Department of Public Welfare. Since then we have received for the years 1957/58,
1958/59 and 1959/60 ending June 30, 1960, additional State funds to carry on our research. In total we received $38,492.00.

Additional research funds of $2,600.00 were received from the Minneapolis and the Minnesota Associations for Retarded Children. The phenylalanine-free diet for the first year (1957/58) was furnished to us gratis from Mead, Johnson & Co., through Dr. James Tuholski, their Associate Director of Clinical Research. This product would have cost $2,400.00, had it been necessary for us to purchase it.

Diet Studies;

The phenylalanine-free food used in our diet studies is an artificial food product prepared from milk casein in which the phenylalanine has been eliminated and replaced by other amino-acids. A special food product of this type which we are using, was developed by Mead, Johnson & Co., and is on the market under the name of Lofenalac.

Presently we have 7 patients of this type on the phenylalanine-free diet - ages 7, 7½, 10, 12, 19, 38, and 46 years. These are matched with untreated numbers of phenylpyruvic patients as controls. Both groups of patients are followed closely and at regular intervals in regard to their metabolism, biochemistry, clinical signs, general behavior, intelligence level and electroencephalograms. Until now, 2 patients have been on the diet for 1½ years, 2 for 17 months, 1 for 9 months, 1 for 6½-months and 1 for 3 months. Our youngest patient (M.Mc.) under study was admitted to the institution in January of 1958 from the waiting list so he could be included in this research. His 10-year-old sister and 2-year-old brother have the same metabolic error a very unusual occurrence. The sister is moderately retarded, but the 2-year-old brother in Dr. Berendes' research group at the University of Minnesota has been on the special diet since he was 6 months old and at present is developing normally.

Research Goals of the Diet Studies:

We are trying to solve the following questions:

1. Is the diet effective also in older patients?

2. How long has this diet to be given to become effective?
3. Which of the biochemical, clinical, psychological and EEG changes are reversible?

4. Is mental deficiency due to a permanent brain damage sustained in the formative stages of early infancy, or is it due to the toxic action of phenylalanine and related metabolites which prevent the brain from functioning normally?

Results of the Diet Studies;

It is too early to draw definite conclusions from our studies, but some preliminary results might be stated:

All our 7 patients, irrespective of age, have reacted favorably to the diet in their metabolism and biochemical data. Within 6 to 8 days of the diet the high phenylalanine level (30-50 mg %) becomes normal (2-4 mg %), the phenylpyruvic acid disappears from the urine. The urine remains negative if the phenylalanine in the diet is not increased above 10-12 mg. per Kg. body weight, and per day.

Muscular spasticity, present in 2 patients, (G.W. and C.E.), has disappeared. A severe eczema in a patient (C.E.) has entirely disappeared. It once flared up during a period of increased phenylalanine intake, but disappeared again on lowering the phenylalanine intake.

She electroencephalograms of the 7 patients on the diet, showing various pathological patterns, were checked in 3 month intervals but so far only 2 (G-W. and M.M.) have changed under the diet.

The synthetic diet 'Lofenalac' is easily prepared and generally well taken by the patients. A 10 year old spastic bed patient (Or. Wa) created periodical feeding difficulties on the diet but these were overcome. A 19 year old boy (G.Wi.) of very low intelligence, after being on the diet for 6½ months, developed a severe rumination and self-induced regurgitation with secondary weight loss so that he had to be taken off the diet temporarily. All other patients show satisfactory weight gain when the 'Lofenalac diet' is supplemented by vegetables, fruits and natural proteins within the permitted tolerance of phenylalanine intake (10-12 mg. per Kilo body weight per day.).
Summary of Diet Studies:

Our diet studies may permit the following tentative conclusions: Older patients react to the diet in their metabolism and biochemistry in a similar way as infants and small children. Skin manifestations and muscular rigidity show the favorable effect on an improved cell metabolism. There appear also, without doubt, favorable personality changes. But the brain damage sustained in the formative stages of early infancy, measured on electroencephalogram and intelligence, appears probably irreversible at this point in the study.

Biochemical Findings and Problems:

1. The phenylalanine values in the blood of normal people are between 0.5 and 1.5 mg %. The values of our untreated P.K.U. patients range between 20-50 mg %. They lie in lower range than those of infants and small children (40-90 mg %) (Armstrong & Low).

2. In most of the patients the phenylalanine level in the serum is pretty stable; but in about 25% of our patients the phenylalanine level showed considerable fluctuation from day to day (also observed by Berendes). This might be caused either by variations in the phenylalanine intake or in the 24-hour cycle of the blood phenylalanine level. This will be the object of further investigations.

3. There exists a phenylalanine threshold of 15-20 mg % in the blood with apparently some individual variations, which determines the excretion of phenylpyruvic acid in the urine.

4. When the phenylalanine in the serum falls to that threshold level, the phenylpyruvic acid excretion in the urine becomes intermittent. This observation, made on 3 of our diet patients, might explain the fact that a certain number of our P.K.U. patients were found to excrete phenylpyruvic acid intermittently. (Intermittent excretion has been reported by Wright and Tarjan, and by Centerwall). We shall also study this problem further, since it is important from diagnostic point of view.
5. The tolerance level for the daily phenylalanine intake in P.K.U. infants and small children is between 15 to 25 mg per kilo body weight per day (Berendes). The tolerance level for our older P.K.U. patients is, in our experience, 10-12 mg phenylalanine per kilo body weight per day. If the phenylalanine intake is increased above this amount, the phenylalanine level rises above the desired level of 5-8 mg % in the blood. (Similar observations Hsia and Knox).

6. Comparative determinations of phenylpyruvic acid in the urine, both with the Dinitrophenyl-hydrazine method (Penrose and Quastel) and the colorimetric ferric citrate method (Kropp and Lang) show the excretion of an unknown keto-acid, other than diacetic acid and acetone. Such a keto-acid has been observed by Woolf and Berry (1952).

7. The accumulation of phenylalanine in liver and brain tissues prevent the normal oxidation of tryptophan and its transformation to serotonin which plays an important role in brain metabolism. The final product in this metabolic chain appears in the urine as 5-hydroxy-indolacetic acid. Berendes reported that the urinary excretion of this acid is decreased in phenylketonuria and increases under phenylalanine-free diet. We intend to study this phenomenon on our older patients.

Genetic Aspects:

This is an inherited disease due to a single recessive, non-sex-linked gene. Two entirely normal parents may carry this abnormal gene. In that case, 25% of their children should be mentally retarded, 25% normal and free of the abnormal gene, while 50% of their children, though appearing normal, should be carrying the abnormal gene and would be regarded as 'heterozygous carriers'. It has become possible to find the carrier in families known to have phenylpyruvic relatives by chemical blood tests and phenylalanine-tolerance tests. We plan to start such tests on blood relatives of our phenylpyruvic patients as soon as we have perfected the paperchromatographic method needed.

The identification of carriers would lend itself to a state-wide study
of the genetic distribution of P.K.U. within our population, and appears of the utmost importance in the prevention of this type of mental deficiency.

Prevention of Phenylpyruvic Oligophrenia:

Our studies prove beyond doubt, how important it is that P.K.U. patients are diagnosed early and placed on a phenylalanine-free diet during the first 2 years, if possible, during the first 6 months of life.

This can be done by methods recommended by the Federal Children's Bureau in Washington, D.C. (Feb. 26, 1959).

1. Repeated urine testing for P.K.U. (with Phenistix) of all infants by all physicians, pediatricians and well-baby-clinics.

2. Repeated urine testing for P.K.U. in all high risk groups (mentally retarded infants and children, all siblings and relatives of P.K.U. patients, all children with convulsive disorder).

3. Determination of phenylalanine levels in blood of doubtful cases.

4. Phenylalanine tolerance tests in high risk groups to identify 'heterozygous carriers' of the P.K.U. gene.