 [2-3-75]

# ANNUAL REPORT TO CONGRESS

This Report is prepared in accordance with the provision of Section 1115 of the Public Health Service Act, as amended.

## BACKGROUND

### Provisions of the Legislation

The Cooley's Anemia Control Act (P.L. 92-414) amended Title XI of the Public Health Service Act to provide for a Federal program of grants to public and non-profit private entities and contracts with public and private entities for (1) "projects for the establishment and operation, primarily through other existing health programs, of Cooley's anemia screening, treatment, and counseling programs." (2) "research in the diagnosis, treatment, and prevention of Cooley's anemia, including projects for the development of effective and inexpensive tests which will identify those who have the disease or carry the trait." (3) "a program to develop information and educational materials relating to Cooley's anemia and to disseminate such information and materials to persons providing health care and the public generally."

The law provides that the Secretary may make a grant for a screening, treatment and counseling program when he determines that the screening provided by such a program will be done through an effective and inexpensive Cooley's anemia screening test.

The Act also provides that the Secretary shall establish a program within the Public Health Service to provide for voluntary Cooley's anemia screening, counseling and treatment. The program shall utilize effective and inexpensive screening tests, shall be made available through the facilities of the Public Health Service to any person requesting screening, counseling, or treatment and shall include appropriate publicity of the availability and voluntary nature of such programs.

A comprehensive report on the administration of this part of the Public Health Service Act is to be submitted to the President for transmittal to the Congress on or before April 1 of each year together with such recommendations for additional legislation as the Secretary deems necessary.

Nature of the Cooley's Anemia Problem

Cooley's anemia is an inherited blood disorder which occurs primarily in persons of Mediterranean ancestry. In the United States most of the victims are of Italian, Greek, Turkish, Southern French or North African descent or origin although the disease is not limited to these groups.

As in many genetic blood disorders, those who inherit the gene from only one parent carry the trait and are usually free of symptoms while those who inherit the gene from both parents have overt disease. This severe form of the disease occurs in about one fourth of the children of parents who both carry the trait. Cooley's anemia is characterized by the production of abnormally thin red blood cells and by a profound anemia which appears soon after birth with severe effects including enlarged spleen and liver and grossly active bone marrow producing thickening of facial bones.

There is no known cure, and the only effective treatment is by blood transfusions usually once a month but sometimes more frequently to alleviate the constantly recurring anemia. A serious complication is an overload of iron in the blood resulting from the frequent transfusions. There are agents with limited effectiveness in removing this excess iron, but those now available are too toxic for general use. Children with this disease often die within a few years while some live into their twenties. Individuals with the trait generally enjoy normal health and life span. The prevalence is not really known. The best available estimate is that about 200,000 persons in the country carry the gene.a/ There is no national estimate of the number of cases of clinical disease, but it is reported that there are 1,000 cases known in New York City.b/

Diagnosis is simple in those who have clinical disease, but definite diagnosis in those who only carry the trait is much more difficult and requires a number of relatively sophisticated hematologic tests. Experts have indicated that there is as yet no simple screening test although progress in this area is being made.

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a/ Person, Howard A., et al, "comprehensive testing of Thallasemia Trait"
b/ Cooley's Anemia Foundation

Organizational Arrangements

Under authority delegated to him by the Secretary, the Assistant Secretary for Health has delegated responsibilities for carrying out the Cooley's anemia program as follows:

(1) to National Institutes of Health the authority for research and development under Section 1111(a)(2);

(2) to Health Services and Mental Health Administration (now the Health Services Administration):

(a) the authority for grants and contracts for screening, treatment and counseling programs under Section 1111(a)(1);

(b) the information and educational program under Section 1111(a)(3); and

(c) activities through other facilities of the Public Health Service under Section 1114.

Coordination of the program effort is carried out by the Assistant Secretary for Health through a Committee represented by his office and each of the two Agencies. This Committee is responsible for recommending policies, facilitating exchange of information, advising on program problems and consolidating reports.

In carrying out its research and development responsibilities, the National Institutes of Health was instructed by the Secretary to establish a research coordinating committee, with membership drawn from NIH Institutes and Research Divisions having responsibility in areas relating to Cooley's anemia. This Committee was charged with the responsibility to (a) develop information on current activities and opportunities in Cooley's anemia, (b) apprise the Office of the Director, NIH, of new activities and opportunities on a continuing basis, (c) develop criteria for the assignment of research grant applications to the various NIH components and review such assignments periodically, (d) provide information and make recommendations on Cooley's anemia research activities, and (e) prepare the research portion of the annual report to the Congress on the administration of the Cooley's Anemia Program, as required by the Act.

In addition, the National Institutes of Health was asked to determine the availability of an effective and inexpensive Cooley's anemia screening test after consultation with experts in the field.

HSA Report

The Health Services Administration (HSA) is carrying out those program activities delegated to it by the Secretary. A pilot program to evaluate screening, education and counseling in Cooley's anemia is planned for fiscal year 1975. This pilot program is being coordinated with a complementary research pilot program in screening and counseling proposed by the NIH.

Planning sessions have begun in coordination with the Sickle Cell Disease Program to review and assess the methodologies determined to be effective in genetic screening, education and counseling programs which closely parallel the Cooley's Anemia problem. This demonstration project should serve as a model or prototype for developing guidelines and maximizing benefits for the Cooley's Anemia Program. This retrospective approach is consistent with the recommendation of the Cooley's Anemia Foundation and the National Cooley's Anemia Advisory Committee. High priority will be in the area of education and counseling activities specifically the development of protocols. Close scrutiny of genetic screening programs and the emerging sociological effects will be influential in determining the overall direction of implementing the service aspect provided by Section 1115 of the Public Health Service Act. The Health Services Administration will continue to define objectives and to develop programs to support all service components of the Act consistent with available resources.

## NIH Report

The "Inter-Institute Coordinating Committee on Cooley's Anemia" has identified high priority research and development areas, and has set up a mechanism to determine the availability of effective and inexpensive screening tests. The 1973 annual report also detailed the research grants supported by the various awarding units of the NIH and outlined the research activities of the Molecular Hematology Branch of the National Heart and Lung Institute (NHLI), where the intramural research in Cooley's anemia is performed within the NIH. The present report shows continued progress in the NIH commitment to the support of research in Cooley's anemia.

## NIH Inter-Institute Coordinating Committee on Cooley's Anemia

The NIH Inter-Institute Coordinating Committee on Cooley's Anemia has continued to function as an effective coordinating mechanism of the NIH research activities in Cooley's anemia. A particularly close cooperative effort has been established between the National Heart and Lung Institute (NHLI) and the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), the two NIH Institutes which have the major responsibility for support of Cooley's anemia research. Useful results are expected in time for next year's report.

## Inexpensive Screening Test and Screening Programs

The subject of the availability of an inexpensive screening test and the need for screening and counseling programs was discussed in great depth at the "Research Workshop in Cooley's Anemia" which was held in New York City in April 1973 by the NIH Inter-Institute Coordinating Committee on Cooley's Anemia. At that time the problems arising from the screening and counseling programs of sickle cell anemia were emerging and, because of the similarity between sickle cell anemia and Cooley's anemia, it is appropriate to utilize the benefits derived from the sickle cell screening programs which can be applied to the programs planned for Cooley's Anemia. Consequently, the Workshop participants recommended, and the NIH Inter-Institute Coordinating Committee on Cooley's Anemia agreed, to postpone development of a mass screening technique until the sociological effects and advisability of a mass screening program were determined by means of carefully controlled, small-scale pilot screening and counseling programs.

Presently available screening techniques for small-scale programs are acceptable but would not be adequate for mass screening. The National Heart and Lung Institute (NHLI) has begun to develop plans for implementing such a pilot research study on screening and counseling for FY '75. This research study is being coordinated with the pilot screening and education and counseling program proposed by the Health Services Administration (HSA).

Development of a More Effective Iron Chelating Agent

Guided by the priorities established by the Inter-Institute Coordinating Committee on Cooley's Anemia, the NIAMDD has this year initiated efforts to develop a safe, more effective iron chelating agent. The need for such an agent arises from the use of multiple blood transfusions to treat victims of Cooley's anemia which leads to damaging and life-threatening iron deposition in the vital organs. The highest priority has been given to the development of such an agent since the one presently in use lacks the desired effectiveness, may have undesirable effects with long-term use, and contributes to the suffering and anxiety of the victims of the disease because of the generally painful route of administration. To move ahead rapidly with these efforts, the National Institute of Arthritis, Metabolism, and Digestive Diseases, has given approximately $150,000 in contracts in FY 1974 to support work on developing new chelating agents. It is hoped that this three year program effort will result in the development of one or more chelating agents that will prove effective and safe enough in animals to then be used in clinical trials in patients.

Presently Active Extramural Research Projects Supported by the NIH

The awarding units of the National Institutes of Health have identified 40 research projects which were active in March 1974. These projects support the research directly related to elucidating knowledge of the specific defects relating to Cooley's anemia and to the understanding of biologic processes associated with Cooley's anemia.

A table, listing these projects and the amount of current support, is appended.

Intramural Research

Research conducted at the National Institutes of Health on Cooley's anemia is carried out in the Molecular Hematology Branch of the National Heart and Lung Institute and is currently funded at a level of $900,000. This broad-based program is exclusively involved in the clinical and laboratory study of hereditary anemias, with a primary interest in Cooley's anemia.

The laboratory portion of the Branch has succeeded in synthesizing human hemoglobin in the absence of intact cells. This cell-free experimental system is composed of purified components isolated from human red blood cells. Using this system, it has been determined that the molecular defect in Cooley's anemia is carried by messenger ribonucleic acid (RNA). Furthermore, the cellular defect of the affected cell can be exactly reproduced using cell-free components from normal cells by the addition of just the isolated messenger RNA molecule from the diseased cell. This is the first time that the molecular defect of a human genetic disease has been reproduced in a cell-free system. The laboratory has recently developed an even more powerful cell-free experimental system in which the messenger RNA itself can be synthesized

directly from affected human desoxyribonucleic acid (DNA). This discovery is considered a major advance towards the future understanding and control of Cooley's anemia. Using this system, it should ultimately be possible to discover the exact cause of the defect which results in Cooley's anemia. In addition to these biochemical studies, the regulation of hemoglobin gene expression in bone marrow cells grown in tissue culture is being studied. The mechanism which controls the switching of one hemoglobin gene to another in the intact cell is being investigated in hopes of being able to "switch off" the defective Cooley's anemia gene.

In the recently created clinical program, patients with Cooley's anemia, sickle cell anemia, and other congenital hemolytic anemias, are treated and studied. A pilot program examining the effectiveness of the iron chelator, desferoxamine, is currently being carried out in the Clinical Center of the National Institutes of Health. Information from this study will be used to help plan national cooperative clinical trials on iron chelating agents.

Summary

In summary new programs have been initiated aimed at a more effective chelating agent and pilot studies in screening and counseling. In addition, support will continue through extramural research projects and intramural programs.

EXTRAMURAL RESEARCH PROJECTS RELATING TO COOLEY'S ANEMIA SUPPORTED BY NIH
ACTIVE AS OF MARCH 29, 1974

| Grant Number | Principal Investigator | Institution | Title of Project | Current Support |
|---|---|---|---|---|
| AM 8154-09 | John F. Bertles | St. Lukes Hosp. Ctr. New York, New York | Genetic Control of Hemoglobin Synthesis | 45,496 |
| AM 9805-08 | Prawase Wasi | Siriraj Hospital Bangkok, Thailand | Thalassemias, Hemoglobinopathies, Related Problems (G6PD) | 15,000 |
| AM 10485-08 | Robin M. Bannerman | Research Fdn. SUNY Buffalo, New York | Abnormalities of Hemoglobin Metabolism | 34,537 |
| AM 12386-07 | Paul Saltman | Univ. of California San Diego, Cal. | Studies on Biological Transport Mechanisms | 41,262 |
| AM 12401-07 | Ronald Rieder | Research Fdn. SUNY Downstate, New York | Protein Synthesis in Erythroid Precursors | 45,351 |
| AM 12895-05 | George Honig | Univ. of Illinois Chicago, Illinois | Regulation of Hemoglobin Synthesis | 19,770 |
| AM 13431-08 | Edward Burka | Thomas Jefferson Univ. Philadelphia, Pa. | Biochemical Determinants of RBC Differentiation | 33,119 |
| AM 13945-04 | Vernon Ingram | Massachusetts Institute of Technology Cambridge, Mass. | Differentiation and Immunology of Erythropoiesis | 69,982 |
| AM 13983-05 | Haig Kazazian | Johns Hopkins Hosp. Baltimore, Md. | The Genetic Control of Hemoglobin | 23,456 |
| AM 14678-04 | Martha Fedorko | Rockefeller Univ. New York, New York | Iron Storage and Mobilization | 17,593 |
| AM 15035-03 | Sherman Weissman | Yale Univ. Med. Ctr. New Haven, Conn. | Hemoglobin mRNA in Thalassemia | 13,271 |

| Grant Number | Principal Investigator | Institution | Title of Project | Current Support |
|---|---|---|---|---|
| AM 15056-04 | Philip Aisen | Albert Einstein Coll. of Med., N.Y., N.Y. | Iron-binding Proteins and Control of Iron Metabolism | 57,233 |
| AM 15322-08 | David Nathan | Childrens Hosp. Med. Ctr., Boston, Mass. | Molecular Basis of Thalassemia | 62,041 |
| AM 15467-03 | David W. Smith | Northwestern Univ. Evanston, Illinois | Transfer RNA and Hemoglobin Synthesis | 18,511 |
| AM 15492-02 | Francesco Conconi | Univ. of Ferrara Ferrara, Italy | Molecular Pathology of Beta-Thalassemia | 11,100 |
| AM 16691-02 | Elias Schwartz | Childrens Hospital Philadelphia, Pa. | Heme and Globin Synthesis in Infants and Children | 44,681 |
| AM 16930-01 | Peter Rowley | Univ. of Rochester Rochester, New York | Hemoglobin Synthesis in Thalassemia | 40,774 |
| AM 17146-01 | John Nielands | Univ. of California Berkeley, Cal. | Chelates for Cooley's Anemia | 42,552 |
| AM 17348-02 | Helen Ranney | Univ. of California San Diego, Cal. | Studies of the Properties of Hemoglobin | 71,947 |

| Grant Number | Principal Investigator | Institution | Title of Project | Current Support |
|---|---|---|---|---|
| HL 11445 | Sarane T. Bowen | San Francisco State College, San Francisco, California | Genetic Regulation of Hemoglobin Synthesis in Artemia | 25,351 |
| HL 12549 | Roger L. Heintz | Iowa State University Ames, Iowa | Peptide Bond Formation and Hemoglobin Synthesis | 29,100 |
| HL 13293 | William V. Zuker | University of Arizona Tucson, Arizona | The Regulation and Modulation of Hemoglobin Biosynthesis | 2,153 |
| HL CA 14960 | David Kabat | University of Oregon Med. Sch., Portland, Oregon | Control of Gene Expression in Differentiating Cells | 23,559 |
| HL GM 15125 | Y. Akira | City of Hope Natl. Med. Ctr., Durarte, Calif. | Molecular Pathology of Genetic Disorders | 75,200 |
| HL 15383 | Abraham Masur | City College New York, New York | Structure and Properties of Six Hemoglobins | 32,371 |
| HL 15460 | Joseph Bonaventura | Duke Univ. Marine Lab. Beaufort, North Carolina | Molecular Adaptation: The Hemoglobin System | 35,690 |
| HL 12526 | Thomas G. Spiro | Princeton University Princeton, New Jersey | Raman Spectra of Hemo Proteins and Related Molecules | 34,652 |
| GM 14552 | Paul Marks | Columbia University New York, New York | Normal and Abnormal Cell Growth: Multidiscipline Study | 46,485 |
| GM 15253 | Arno Motulsky | University of Washington, Seattle, Washington | Genetics in Medicine | 137,718 |

| Grant Number | Principal Investigator | Institution | Title of Project | Current Support |
|---|---|---|---|---|
| GM 15419 | Donald Rucknagel | University of Michigan, Ann Arbor, Michigan | Cellular and Biochemical Genetics | 114,872 |
| GM 17702 | Jarvis E. Seegmiller | University of Calif. San Diego, California | Human Biochemical Genetics | 54,588 |
| GM 19443 | Kurt Hirschhorn | Mount Sinai School of Medicine, New York, New York | Clinical Genetics Ctr. | 12,999 |
| GM 19489 | Samuel H. Boyer | Johns Hopkins Baltimore, Maryland | Study of Human Genetics | 12,331 |
| GM 20124 | Leon E. Rosenberg | Yale University New Haven, Connecticut | Center for Human Genetics | 30,127 |
| HD 00254 | Seldon E. Bernstein | Jackson Laboratory Bar Harbor, Maine | Neonatal Blood Disorders | 36,034 |
| RR 125 | Nathan Lassman | Yale University New Haven, Connecticut | Endocrine Manifestation of Iron Storage Associated with Thalassemia Major | 7,358 |
| | Howard Pearson | Yale University New Haven, Connecticut | The Effect of Transfusion Therapy in Thalassemia Major | 1,051 |
| | Howard Pearson | Yale University New Haven, Connecticut | Immunologic Studies in Cogenital Hemolytic Anemias. The Role of the Spleen in Antibody Production | 11,562 |

| Grant Number | Principal Investigator | Institution | Title of Project | [illegible] |
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| RR 125 Cont.) | Richard O'Brien | Yale University<br>New Haven, Connecticut | Ascorbic Acid Enhancement of Desferrioxamine Induced Urinary Iron Excretion in Thalassemia Major | 11,387 |
| RR 128 | David G. Nathan | Children's Hospital<br>Boston, Mass. | Studies of Metabolism of Human Blood Cells (Thalassemia, Sickle Cell) | 26,277 |
| RR 84 | P. Wedemeyer | Children's Hospital<br>Pittsburgh, Pennsylvania | Effectis of Hypertransfusion in Thalassemia | 20,175 |
| RR 86 | Carol Hyman | Children's Hospital<br>Los Angeles, Calif. | Transfusion Therapy in Thalassemia Major | 57,284 |
| RR 73 | Jack Alperin | University of Texas<br>Galveston, Texas | Comparative Study of Erythrocyte Metabolism in Thalassemia, Hereditary Persistence of Fetal Hemoglobin and Hemoglobinopathies | 14,365 |

1/ Total: $1,560,365

1/ The dollar amounts shown for support are direct costs only. An additional amount of $535,205 must be added for indirect costs. The total amount of these awards, therefore, is $2,095,570.

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The letter before each grant number designate the NIH Institute or Division which made the award:

AM - National Institute of Arthritis, Metabolism, and Digestive Diseases
HL - National Heart and Lung Institute
HD - National Institute of Child Health and Human Development
GM - National Institute of General Medical Sciences
RR - Division of Research Resources