It is a pleasure to have a chance to talk with you about our new research program. First, let me tell you about an activity of the National Foundation which, to me, is very important - and I doubt if you have ever heard of it. Last year, I spent a sabbatical leave from Columbia University at the School of Hygiene and Public Health of Johns Hopkins. While there, I was offered this new position. At first, I almost said "no", for what could be done about birth defects? After further discussion with Dr. Thomas Rivers and Dr. Theodore Boyd, it became obvious that I knew nothing about several hopeful leads already known, nor of many more to come. The future sounded so challenging that I accepted the position overnight. The next day, I ventured forth to buy some modern texts on bacteriology and virology, a specialty that did not even exist when I was in medical school. I found two beautiful books, lavishly illustrated, on fine paper, and of such quality that you knew they were already classics the day they were published. From the size of them, I expected them to be $15 or $20 each, and so was pleasantly surprised that one cost $7 and the other $8.00. Not until I joined the National Foundation on July 1st did I find that you - The Foundation - paid a similar amount each time a book was sold. In all 85 American medical schools, these two volumes are recommended to the second year medical students. Thus, you are directly aiding in the training of all the young physicians in this country.

We know that you are vitally interested in the research program. In the recent survey conducted by the Columbia University Institute of Public Opinion, one of the questions asked of 3000 people in 30 different parts of the United States was "How do you think the National Foundation funds should be spent - for medical care, professional education, or research"? 67 per cent answered "Research should come first".

Polio research, of course, continues. The Salk vaccine is very good, 90 to 92 per cent effective in preventing paralytic polio, but we wish that figure were 100 per cent. Efforts to improve its potency and to determine the best dosage schedules are constantly under way. The Sabin live-virus polio vaccine research is continuing. The safety of this oral vaccine for people of all ages seems to be established, though there are still questions about the capacity of Sabin vaccine virus strains to regain virulence after passing through several human intestinal tracts. The degree of its efficiency in preventing polio awaits analysis of reports received from all over the world. Early reports from Esthonia and Lithuania are very encouraging. Until such time as the safety and efficacy of a live-virus vaccine has been proven beyond doubt, and one becomes licensed, of course the Salk vaccine should be administered to everyone, especially to those between six months and 40 years of age.

Research on ECHO and Coxsackie viruses continues, with the production of many new antisera against the many types, by Dr. Herbert Wenner of Kansas City. These antisera are sent all over the world by you, The Foundation, to help in the diagnosis and study of these infections.

Research in rheumatoid arthritis is especially difficult. So far, no animal has been found to which the disease can be given, and thus studied. There is, at present, no experimental model. Substantial funds are being invested in the study of methods of attacking this disease. Rheumatoid arthritis is closely related to other connective tissue diseases such as scleroderma and lupus erythematosus. Many patients with rheumatoid arthritis have been found to have a protein in their blood not found in people who do not have the disease. Whether this protein is part of the cause, or an effect, of the disease, is not known. At present, it is thought that the patient himself may produce some substance, to which his body then reacts adversely, causing the disease symptoms. It is quite possible that research in rheumatoid arthritis will lead to the solution of some problems common to all allergic diseases.

Naturally, research in birth defects interests me more than the other two fields. I have had the good fortune to be present at over 17,000 deliveries in the past 28 years. About 16,000 of these births resulted in normal children. One thousand did not. I know all too well the sinking feeling the doctors and nurses have when the mother's first question must be answered - "No, your baby is not normal". About one half of the defects can be diagnosed in the delivery room. The other half become apparent during the first year of life. Last October, we were given a grant of money to make a movie for physicians and nurses showing how certain defects can be diagnosed within the first 10 minutes of life, even though the abnormalities do not show in the appearance of the baby. About half of such internal defects can be treated successfully with surgery the first day or two of life.

Much research has been done in animals in the field of teratology. Many substances are known which will lead to defective young in many species. We must be very careful not to jump to conclusions that the same results will hold true for human babies. Animal experiments have been very useful in indicating at what time in its development an embryo is apt to be damaged. We know that in human beings it is unlikely that a defect can be produced later than three months after an egg has been fertilized by a sperm. In fact, the main structure of the developing nervous system is completed four weeks after fertilization. Whether or not spina bifida will be present is definitely decided by the end of the <u>first</u> month. Defects in other systems may still take place a little later. It would be very desirable to have a truly early test for pregnancy, one that is accurate 24 to 48 hours after fertilization, so that more might be done to avoid known hazards.

At present, only a few influences during pregnancy are definitely thought to be responsible for human birth defects. There is strong suspicion that exposure to <u>radiation</u> in early pregnancy is not good. The results of pregnancies in progress at the time of the bombing of Hiroshima are not yet known because of the frequency of first-cousin marriages

among the Japanese. Consanguinity is known to increase the number of defective offspring. Neel and Schull are in the process of separating the influence of intermarrying and the influence of the atom bomb. It is advisable not to have elective x-ray studies during the first three months of pregnancy. Gastro-intestinal series and x-rays of bladder and kidneys should be done only if definitely indicated.

One virus disease, german measles, or rubella, when it infects a mother-to-be during early pregnancy, has a 30 per cent chance of causing an abnormal infant to be born. Recent results indicate that there is no relation between the presence of infection with Asian flu, polio, ECHO virus and birth defects.

Another infection, toxoplasmosis, caused by a protozoa, when it affects the mother in early pregnancy, seems to be related to subsequent malformations in the infant.

One strong chemical substance, sometimes used to produce abortion, is frequently associated with the birth of an abnormal baby if abortion does not occur. Dr. Thiersch, who has done much of the research with this drug, feels that if abortion fails, surgical removal of the embryo is mandatory.

Certain maternal factors have been blamed for producing abnormalities in infants, but there is no proof whatsoever that one causes the other. These are shock, worry, anxiety, tension, diet, alcoholism, anesthesias and operation, and airplane flights.

Three approaches to solving the cause of birth defects are under way. The first is a genetic approach. Since the normal number of chromosomes in humans has finally been agreed upon - 46 - more and more chromosomal abnormalities are being found. For example, all mongoloid children, with severe mental deficiency, who have been examined, have been found to have an extra chromosome. But not all people with 47 chromosomes are mongols.

Both men and women have been found who have an extra X chromosome. About half of these are below par mentally. Another type is missing an X chromosome, and is unable to reproduce. Chromosome studies are carried out by tissue culture technics very similar to those used for virus studies. These have been developed, especially by Dr. T.T. Puck, a National Foundation grantee, at the University of Colorado. In addition to being able to count the number of chromosomes in cells, it has been possible to determine some agents that damage chromosomes. X-rays and ultrasonic rays are two such agents. It is very possible that once more ways in which chromosomes are damaged are known, preventive measures will be developed. It is already possible to protect small laboratory animals from fatal doses of x-rays by certain drugs.

A second approach is a chemical one - a chemical called nucleic acid has been found to be not only the active and infective part of viruses, but also to be the backbone of chromosomes. Research in the structure of nucleic acids, such as the study being carried out by another National Foundation grantee and Nobel Prize winner, Linus Pauling, may lead to a chemical interpretation of the biological phrase "mutation of a gene". It is possible that such mutations of gene particles are nothing more than errors in the arrangement of a few atoms in the chemical structure of a nucleic acid molecule. This kind of research is especially difficult and slow to show results, but most exciting for it is closely related to the origin of birth defects.

A third approach is concerned with the relation of environmental factors to incidence of a disorder. Epidemiology, as this method is called, used to be concerned with epidemics, but these are now almost a thing of the past. Epidemiology is more concerned now with chronic diseases, such as coronary disease, diabetes and schizophrenia, with diseases of aging such as arteriosclerosis, and with birth defects. Why is the universally fatal brain and skull anomaly, anencephaly, 20 times as common in Belfast as in Paris? Why is it almost absent in Central Africa? Why are congenitally dislocated

hips so common in Birmingham, England? This last year it was shown in New York state that a high incidence of birth defects occurred in areas in which the rocks had high radioactivity. Painstaking observation, record keeping and analysis may solve some of the mysteries in this field.

These are the present approaches. So far this year, $700,000 has been awarded for research in birth defects. We need new ideas even though they may be costly to develop. A two-pronged drive is under way. One prong is being used to get able, well-recognized research scientists to turn their attention now to the pressing problems of cause and prevention of birth defects. The other is aimed at stirring the imagination of young scientists to find unexpected new paths to follow. With the funds from the March of Dimes we shall supply them with the personnel and materials they need.

The money spent on basic research is granted by national headquarters only after approval by Medical Advisory Committees consisting of nationally recognized scientists and educational leaders. At our meeting last month, 70 such men served as volunteers on these committees. Among them were four University Presidents and seven Deans. Only after earnest discussion and thoughtful consideration by these men are applications for grants approved.

You may well be discouraged by the size and complexity of this problem. I am not at all discouraged. After seeing what was accomplished by the Foundation between 1938, when a polio virus had just been seen, and the present day, when a polio epidemic is almost and could be a thing of the past, I have the greatest confidence that we can solve the riddle of why birth defects occur, and how to prevent them.

Some day, when you read that "the cause of cleft palate has been found", that "club feet need not exist" or that "protection against radiation has been found", you will be thrilled, because you know you voluntarily chose to put your efforts and money into the March of Dimes, and helped hundreds and thousands of other people to come to the same decision.