

protein loss with the development of generalized edema. Complications in severe cases include hypertension, malnutrition, anemia, infection and occasional vascular collapse. In children, about one-third heal spontaneously. Recently corticosteroid therapy and careful management appear to have improved survival rates. In adults with this disorder, the outlook is even more serious. Spontaneous healing is not common and progressive renal failure usually ensues.

5. Pathogenesis of Nephrotic Syndrome and Chronic Glomerulonephritis

The underlying causes of these renal diseases are not known. There is much evidence to indicate that immune mechanisms are responsible, but the precise sequence of events is not clear. The application of safe biopsy techniques, sophisticated biochemical methods and electron microscopy to the study of glomerular lesions has helped unravel this complex group of disorders. The application of new immunological concepts, combined with transplantation studies may finally yield answers to the remaining basic questions about these diseases.

6. Lupus Nephritis

Systemic lupus erythematosus is a generalized disease involving the kidneys, brain, lungs, skin, joints, and other organs. Nearly 300 deaths were listed in 1964. It is predominantly a disease of young women, but attacks both sexes through a wide age range. The incidence has increased markedly during the past two decades partly because of improved methods of diagnosis and almost certainly because of the more widespread use of sensitizing drugs. There is much evidence that an abnormal immune response, precipitated by a variety of agents, is responsible for this disease.

Renal involvement in patients with systemic lupus erythematosus is perhaps the most ominous of the many manifestations of the disease. In general, renal involvement is found in about two-thirds of lupus patients. Patients who exhibit renal involvement usually do so early in the course of their disease. The renal lesions run the gamut from a local glomerulitis involving parts of glomeruli, to a focal lesion involving some glomeruli, to generalized subacute or chronic glomerulonephritis, with or without the characteristic wire-loop lesion.

Clinical manifestations of renal lupus include hypertension, edema, and on occasion oliguria or anuria with rapidly progressing uremia. Many patients with lupus nephritis show at some stage the nephrotic syndrome. Usually, this group does poorly.

Corticosteroids have become a mainstay of lupus nephritis therapy, though there are divergent opinions as to the effectiveness of these drugs in various stages of the disease. Recently antimetabolites have been used and present information suggests a significant measure of success. Additional information about the nature of the renal changes in this disease has been obtained by attempts to relate ultrastructure and functional derangements. Studies are under way to elucidate the role played by plasma proteins in the evolution of this disease. Important work is being done correlating the histologic changes in the kidney with clinical course. Understanding of the pathogenesis of this disease has important implications for all hypersensitivity diseases such as rheumatoid arthritis, all chronic nephritis and rheumatic fever and has relativity to transplantation immunology.

D. Other Related Renal Diseases

Many kidney diseases and other diseases which often lead to severe renal disease were not included in this initial analysis. These are described briefly in this section.

1. Polycystic Disease of the Kidneys

This disease is by far the most important of the developmental anomalies of the kidneys. This anomaly was held responsible for 1,061 deaths in the United States in 1964. In this group over three-fourths of the deaths occurred before the age of 60. This disease masquerades in a variety of forms including vascular accidents, hypertension, pyelonephritis and chronic renal failure. There are two forms: one inherited as a dominant trait which usually becomes manifest in adult patients, and one which appears to be inherited as a recessive trait primarily manifested in children. A history of polycystic disease is usually readily obtained in other family members; unfortunately in some families there is a pathetic desire to hide the trait. Conventional treatment helps these patients. But, as end-stage renal failure approaches, hemodialysis and eventual renal transplantation are their only hope for survival.

2. Gouty Nephropathy

An estimated 250,000 people in this country are suffering from some form of gout. In 1964, 130 deaths were attributed to gout. In the advanced stages of gout one of the major causes of death is renal insufficiency. Some reports suggest that albuminuria occurs in up to 40% of patients with gout, renal calculi in 17% and that the development of renal insufficiency in 18% of cases. The only distinctive pathologic feature of the gouty kidney is the presence of urate crystals. The precipitation of this material in the kidney may be responsible for the frequently observed

pathologic picture of pyelonephritis or nephrosclerosis and less often amyloidosis.

Management of gout has until recently been limited to the relief of joint symptoms primarily through the use of colchicine and the reduction of elevated blood uric acid levels by increasing uric acid excretion primarily through the use of probenecid. A new approach to reduction of blood uric acid levels has been provided by the introduction of allopurinol, a xanthine oxidase inhibitor, which acts by decreasing the production rather than the excretion of uric acid. Important avenues of investigation have been opened not only in primary gout but in other diseases associated with increased uric acid levels. The promise of reduction in morbidity and mortality from gout is great.

3. Hypercalcemia

Hypercalcemia from a variety of causes may produce secondary renal disease which if uninterrupted is often lethal. Calcification of the kidney tissue, formation of stones, and secondary pyelonephritis are common in advanced cases and usually lead to end-stage renal failure. Such diverse entities as hyperparathyroidism, sarcoidosis, vitamin D intoxication, excessive ingestion of milk and alkali, and immobilization in bed can lead to hypercalcemic nephropathy. In many of these cases therapy directed at the underlying problem is successful in arresting the progress of renal damage. Often, however, the process is not recognized until renal damage has progressed to an advanced state. In this stage, particularly if hypertension has supervened, reversal of the process is usually impossible and terminal renal failure ensues.

4. Diabetes

As the life span of diabetics has increased, renal disease has become an increasingly important cause of morbidity and mortality. The renal complications of diabetes are manifold and include acute and chronic infection, renal arterio-sclerosis and arteriolar sclerosis with hypertension, and finally intercapillary glomerulosclerosis, a process seen only in association with diabetes mellitus. Renal diseases account for over 10% of the deaths in diabetics.

The management of these renal problems is only moderately successful. Eradication of urinary tract infection is particularly difficult in diabetics, but should be pursued with vigor since this may retard the progress of renal damage and prevent septicemia. Hypertension may be ameliorated by conventional therapy.

Unfortunately, chronic hemodialysis and transplantation offer little chance for long-term survival in most of these patients since severe arterial disease is usually widespread in affected patients. Better understanding of the mechanisms of development of atherosclerosis and of lipid metabolism and changes occurring in the capillary basement membrane offer the best hope for improving the outlook of these patients.

5. Miscellaneous Renal and Renal Related Diseases

Many other diseases are of importance in any discussion of kidney diseases. Malignant diseases of the prostate account for over 15,000 deaths annually. In this usually indolent malignancy early detection may cure many patients, while hormonal therapy will help others. Prompt treatment of renal infections and alleviation of urinary obstruction reduces renal deaths. Benign prostatic hypertrophy leads to urinary tract obstruction with frequent development of hydronephrosis and pyelonephritis.

New cryosurgical techniques are promising for this group and there is indication that hormonal therapy may be beneficial.

Kidney Stones often lead to obstruction and infection. In cases due to gout and hypercalcemia the treatment of the underlying disorder may be effective. In other cases the cause is not clear, but may be related to individual habits or peculiarities of the environment. Recent identification and isolation of an "anti-stone substance" which is absent in the urine of some who develop kidney stones may lead to new therapeutic methods. In still other cases, such as cystinuria and oxalosis, the metabolic defects have been identified and corrective therapy may be forthcoming.

A number of urinary tract anomalies are lethal in infancy. Other obstructive and muscular lesions may respond to treatment in later life.

Tuberculosis of the genitourinary tract still accounts for almost 100 deaths per year and if recognized may respond to a variety of measures. Toxemias of pregnancy still account for over 200 deaths per year. Renal amyloidosis secondary to rheumatoid arthritis, ulcerative colitis and leprosy accounts for many deaths. Amyloidosis of the kidney due to chronic infectious diseases is a major world cause of renal deaths.

E. Acute Renal Failure

Acute renal failure may appear suddenly following a massive kidney injury or develop in the course of a chronic renal disease. In either case urine flow is greatly diminished and the kidneys are temporarily unable to perform their usual functions. The incidence of acute renal failure is difficult to determine, however, in one university referral center, acute renal failure accounted for half of the patients seen with uremia. In a nationwide sample

the proportion of patients with uremia who present with acute renal failure would probably be much lower.

Acute renal failure may be due to a number of causes including insufficient renal blood flow, transfusion reactions from mis-matched blood, fulminating infections, kidney poisons, acute urinary tract obstruction and acute glomerulonephritis. Prompt restoration of blood flow, relief of obstruction and effective treatment of infection are essential in preventing further renal damage. Toxic substances must be immediately identified and measures taken to remove them by dialysis or chemical binding whenever possible.

After all available measures have been taken to arrest further damage, assessment of the degree of damage must be undertaken and management planned. In a few cases the damage is mild and no further measures are necessary. In others, renal function ceases completely and the patients must be sustained by a combination of dialysis and dietary regulation while healing takes place. In these cases after a period of days or weeks the kidney gradually resumes its function and may eventually show return to normal function.

Broad advances in our knowledge of kidney function, wide use of hemodialysis and availability of remarkable new therapeutic agents have resulted in a gradual increase in the number of patients surviving. Now over 50% of patients with severe acute renal failure recover.

In other patients kidney damage is too severe and effective renal function does not return. Some die of other underlying processes or infection while others have little or no return of function and enter a period of chronic renal failure.

F. Chronic Renal Failure

Despite current screening programs and early medical intervention in many cases of renal diseases, many patients do not seek medical attention

until irreversible renal damage has progressed to an advanced state. Often destructive kidney lesions are painless and indeed asymptomatic. Symptoms may not be noticed by the patient until 50 to 80% of his kidneys have been destroyed. If at this point the patient seeks the help of his physician it may still be possible, depending on the underlying disease, to arrest renal destruction, prolong life and reduce complications. For example, in chronic pyelonephritis due to bacterial infection, relief of obstruction or removal of stones combined with selective antibiotic therapy may arrest renal destruction and in lupus erythematosus steroid and immunosuppressive therapy often retard the progress of renal destruction. In other cases such as chronic glomerulonephritis, congenital polycystic disease, diabetic glomerulosclerosis, and some cases of chronic pyelonephritis, there is no current effective therapy to arrest renal destruction.

1. Dietary Therapy

In these cases careful intelligent management has much to offer. Three major kidney functions are the regulation of water and electrolytes, the excretion of nitrogenous waste products and the excretion of excess acid. By careful regulation of dietary intake of sodium and potassium, restriction of protein intake to a minimum balanced mixture of essential amino acids, and limitation of the acid forming potential of the diet it is possible to reduce considerably the morbidity of patients with chronic renal failure. In cooperative patients, the frequency of dialysis can be greatly reduced. Anemia, hypertension and certain metabolic disturbances remain severe problems in some patients.

2. Hemodialysis and Transplantation

In those patients who have progressed to the end-stages of renal failure or who have other threatening complications which can no longer

be managed by selective management of intake, chronic hemodialysis and renal transplantation now offer a new hope for survival. Because experience is limited, it is difficult to predict the eventual applicability of these two procedures to the total population with end-stage renal failure. Further research into improved dialysis membranes, combinations of hemodialysis with various ion exchange methods and/or selective adsorption procedures, and better understanding of complex metabolic problems will reduce the morbidity and mortality associated with hemodialysis and may yield entirely new methods with wider application and reduced cost. Home dialysis is promising. In the field of organ transplantation experience in management of transplant recipients and improved matching of donor kidney and recipient have resulted in substantial reduction in morbidity and mortality. Now this procedure is performed with remarkable success in a number of centers. Further advances in histocompatibility typing, selective immunosuppression and patient management can be expected.

a. Hemodialysis

Hemodialysis has been used with success in acute renal failure since 1947. The development of the indwelling arteriovenous shunt in 1960 made possible the use of intermittent hemodialysis to prolong life in irreversible uremia. In the current state of the art, a number of problems are apparent in the application of this procedure.

b. Factors Limiting Application of Hemodialysis

Partly because of limited facilities and personnel and because of the limitations of current techniques, experience has largely been limited to patients between ages 20 and 55. Unfortunately, about three fourths of patients reaching end-stage renal failure and who thus might benefit from hemodialysis are beyond the age of 60.

Within the mid-age group, psychological problems have presented a serious obstacle to some who might have benefited from hemodialysis. A number of patients have developed problems in accepting their dependence on dialysis machines and their attending medical personnel while others have suffered a change in self image which has led to serious social difficulties. The motivation and intelligence of the patient are crucial to success.

The medical problems associated with chronic hemodialysis are formidable. Peripheral neuropathy and metastatic calcification are common. Hypertension is often difficult to control. The anemia of chronic renal failure often requires transfusions which eventually may lead to hemosiderosis. Serum hepatitis is a danger to the patient and the attending personnel as well. Infection at the cannula site and clotting of the cannula are persistent problems. Severe metabolic bone disease is still frequent although some progress has been made in its control. Human errors and mechanical difficulties are occasionally responsible for failures. Well trained, highly motivated and experienced medical personnel are scarce.

Despite these problems many live useful, productive lives. While extension of hemodialysis to older age groups presents difficult problems, technical improvements and increased experience may prove intermittent hemodialysis feasible in some older patients. Intermittent hemodialysis combined with dietary therapy may prolong useful life in many and sustain others who might benefit from renal transplantation.

Clearly, many now face death who could be helped by intermittent hemodialysis.

c. Kidney Transplantation

Renal transplantation offers another future hope for those afflicted with end-stage renal failure. Currently 30-month survival rates range from 17 to 47% for patients with cadaver transplants and 60% or more for living related donors. In cases where a good histocompatibility match has been obtained and no rejection crisis has occurred in the first few months after transplantation, good renal function has been reported in up to 93% of patients after three and one-half years.

d. Limitations

Aside from the operative morbidity and mortality associated with renal transplantation there are currently several major obstacles to greater use of renal transplantation for end-stage renal failure. The availability of viable human kidneys presents a major problem. The use of living related donors raises serious moral questions and such donors will provide only a limited number of kidneys. Cadaver kidneys are a major potential source of viable kidneys; however, the problems of histocompatibility matching, the ethical and legal questions of consent, and the logistical problems of preservation and transportation have not yet been solved. Immunosuppressive therapy has been successful in preventing homograft rejection in many cases, but has often led to serious and sometimes fatal infection in the recipient. Although the development of more selective immunosuppressive agents has been promising, the problem of complicating infections has not been overcome.

Large areas of investigation offering significant conceptual advances in the field of tissue transplantation remain to be explored. Induction of adult tolerance, detailed analysis of histocompatibility

antigens and work on the non-immunologic mechanisms of cell to cell interaction are some of these.

e. Peritoneal Dialysis

Peritoneal dialysis offers a useful, but a present limited alternative to hemodialysis. Exchange of chemicals is less efficient, leading to longer treatment periods than with hemodialysis, and infection remains a major obstacle. Intermittent catheterization, new flexible catheters, and automated flushing have improved this method.

F. Poisoning

In 1964, over 1,000 deaths resulted from accidental poisonings from salicylates, barbiturates and other analgesic and soporific agents. In addition, over 2,400 suicides resulted from use of these agents. Hemodialysis techniques are of great value in most of these poisonings and it is reasonable to assume that a significant number of these deaths could have been avoided if personnel trained in the techniques of emergency hemodialysis had been widely available.

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Current Kidney Disease Control Programs

I. INTRODUCTION

This chapter is devoted to a brief description of current kidney disease "program" activities and deficiencies. "Program" as used herein refers to an organized effort directed toward the eradication or alleviation of kidney disease problems. Kidney disease program efforts may have an active nature, such as a research project in kidney disease, or passive nature such as a hospital renal clinic.

Kidney disease program efforts in this chapter are viewed from the standpoint of program source and by program objective. Program source is considered in terms of federal and nonfederal. The latter includes state and local government, individual, philanthropic, and nongovernment institutional financial expenditures for or on behalf of kidney disease.

Kidney disease programs objectives may be separated into the following functional areas:

- 1) Research--Includes laboratory and clinical investigations and developmental research efforts.
- 2) Other Methodological Studies in Kidney Disease--Includes operational studies, screening and detection programs, and demonstration projects.
- 3) Treatment--Includes hospital, nursing home, physician and other professional services for diagnosis and therapy of kidney diseases.
- 4) Facilities--Includes aid in construction, remodeling or expansion of facilities for activities in kidney disease treatment, research, and training.
- 5) Education and Training--Includes basic education (fellowships),

specialized on-the-job training (training grants), and postgraduate education in kidney diseases.

The ability to describe many federal and particularly nonfederal kidney disease program efforts in terms of expenditures is highly variable because of insufficient or inadequate data. In many instances kidney disease program efforts are merged with others thereby making it difficult to proportion accurately kidney-related expenditures among general programs. In some instances it was necessary to use data for the year 1964 because of its completeness and availability. Whenever possible, programs for more recent years are used in order to make this document action-oriented for imminent budgetary periods, and to take into consideration increased efforts in this disease area.

II. SPECIFIC FEDERAL KIDNEY DISEASE PROGRAM EFFORTS

A number of federal agencies are currently active in kidney disease. Some have primary responsibilities in providing patient care and others are interested in basic and developmental research. As in most other diseases, there is no single federal agency charged with the responsibility for kidney disease programs. PHS recently indicated that there is no comprehensive plan for coordinated attacks against kidney disease because:

- 1) Kidney disease is notoriously difficult to pinpoint as a cause for morbidity and mortality in the population;
- 2) The variation in opinion within the medical community as to the desirability of large-scale dialysis and transplantation efforts;
- 3) The need for more time to improve and develop research; and
- 4) No single agency or organization has taken on itself the

leadership in bringing together all interested groups in kidney disease.

Kidney disease program activities of specific Federal Agencies follow.

A. U. S. Department of Health Education and Welfare (HEW)

HEW has undertaken major responsibility of kidney disease control programs in the U. S. Its activities range from laboratory and clinical research performed or supported by the National Institutes of Health (NIH) to support of dialysis center demonstration projects by the Kidney Disease Control Program of the National Center for Chronic Disease Control. Specific groups and activities follow.

1. National Institutes of Health (NIH)

a. National Institute of Arthritis and Metabolic Diseases (NIAMD)

NIAMD's primary efforts are in the area of laboratory and clinical research and in urology and kidney diseases in general, and research and development in chronic uremia, hemodialysis and artificial kidney development.

The NIAMD has traditionally invested major funds in extramural support of laboratory and clinical research in kidney diseases and urologic disorders. It was a group of Institute grantees that developed the permanently indwelling polymer shunts which made chronic intermittent hemodialysis possible. The emergence of this new treatment modality encouraged the Congress, in the summer of 1965, to appropriate funds to this Institute for the pursuit of a centrally directed program of research and development in chronic uremia, hemodialysis and artificial kidney development, utilizing predominantly a direct contract approach as well as increased research grant support.

A thorough study of the state of the art made it apparent that no single specific direction should be followed which would exclude others which might be relevant. Several different types of

artificial kidneys are in use at the moment, and different methodologies are being advocated by the various workers in the field. Therefore, at this time, a variety of approaches in artificial kidney development are being supported. Once it becomes evident that one or more approaches show greater promise, efforts will be concentrated in these directions.

The Artificial Kidney-Chronic Uremia Program was mounted with the placement of carefully selected research and development contracts with universities, nonprofit research laboratories and industrial concerns which possessed relevant talents and facilities. These projects involve development of improved blood cannulas; evaluation and development of new polymer surfaces for artificial kidneys; cannulas and membranes which do not induce blood coagulation; design of more efficient, compact, and less costly dialyzer systems; development of a new concept of artificial kidney dialysis ("hollow fiber" or "capillary" kidneys); research on and development of absorption cartridges for blood purification; research on the utilization of ultrasonics to speed up dialysis in artificial kidneys; development of inexpensive disposable dialysis units; improvement and design of new dialysis units with automated failsafe mechanisms; design and development of a prototype for a portable artificial kidney; evaluation of a special protein restricted diet in the maintenance of uremic patients for whom chronic dialysis

is deemed not feasible or unobtainable; isolation from dialysates and identification of the as yet unknown compound(s) which is (are) specifically responsible for the toxic symptomatology in uremia; and many other projects related to improved dialysis methodology or apparatus.

An important new activity involves the establishment of a long term central patient registry and medical information system involving all patients maintained with the aid of chronic dialysis in the United States (and, through cooperation of the European Dialysis and Transplant Association, of similar patients in Europe). This activity, which involves very close collaboration with the Kidney Disease Control Program of PHS and with the Veterans Administration, will permit a comparative evaluation of different dialysis treatment methods and equipment based on a longitudinal study of all patients involved, from their selection for chronic dialysis treatment onward.

The portion of the program which is funded by extramural research grants complements closely the contract program described above, but is oriented more toward elucidation of clinical and fundamental biological problems related to the treatment of chronic uremia rather than toward hardware development. It involves studies on urea metabolism in uremic patients undergoing chronic dialysis; the effectiveness of peritoneal dialysis in uremia patients; other novel approaches to blood purification in chronic kidney failure such as dialysis of a surgically relocated, isolated intestinal loop, lymph dialysis and dialysis in the home; and the nature of the biochemical defects in advanced uremia.

A summary of NIAMD kidney disease program expenditures is presented in Table I.

Table I

NIAMD KIDNEY DISEASE PROGRAM EXPENDITURES FOR 1966

Program	1966 Expenditures
Research and Development:	
Artificial Kidney and Dialysis	\$3,151,000
Kidney Transplant Research	593,000
Other Renal and Urology Research	<u>2,894,000</u>
Total	\$6,638,000

b. National Institute of Allergy and Infectious Diseases (NIAID)

NIAID's efforts are devoted to fundamental research and applied research and development in kidney transplantation including typing systems, immunosuppression and organ preservation.

Grant-supported research projects, intramural studies, and organized developmental work in medical centers and industry have been stepped up in recent years.

The urgent need, and the short-term goal, of the tissue transplantation immunology program is the identification of all the tissue transplantation antigens and their classification according to relative strength. Experimental work has shown that there are apparently only 6 to 10 major transplantation antigens rather than the 15 to 30 which had been predicted on the basis of animal studies.

Certain immunosuppressive drugs for use in the prevention or control of the rejection phenomenon are being studied. Studies are being conducted to find more effective and less toxic drugs to control the immune response.

Two groups of investigators have produced specific immunologic

tolerance to grafts in mice and in dogs by administration of anti-lymphocyte serum before the transplant operation. This procedure resulted in striking prolongation of the graft and apparently induced tolerance also to second grafts. Another group found that antiserum to thymus prolonged skin graft survival in rats twice as long as antiserum to lymphocytes.

In addition to antilymphocyte serum, total and sub-total body irradiation, cytotoxic drugs, and surgical alterations of the lymphatic system have been used in attempts to reduce or eliminate the lymphocyte population and thus increase tolerance to homografts. These methods, however, also cause undesirable general effects, such as depression of bone marrow and red blood cell formation.

Paralleling the efforts to develop reagents, tests, and techniques for applying the knowledge already gained are research projects aimed at understanding the basic immunologic processes of the human body. Intramural projects in Bethesda on immunology focus on such areas as hypersensitivity, mechanisms of the immune response, immunochemistry of serum antibodies and antisera, and induction of delayed hypersensitivity. Many of these studies are closely related to the problems of transplantation. Fifty-nine research grants and fifteen collaborative research contracts were supported in 1966. A summary of NIAID kidney disease program expenditures for 1966 is presented in Table II.

Table II
NIAID KIDNEY DISEASE PROGRAM EXPENDITURES FOR 1966

Program	1966 Expenditures
Intramural Research in Transplantation Immunology	\$ 190,000
Research Grants--Transplantation Immunology	3,100,000
Collaborative Research Contracts-- Transplantation and Immunology	<u>849,000</u>
Total	\$4,139,000

c. National Heart Institute (NHI)

Through the years, the National Heart Institute has supported a wide variety of basic and applied research in kidney diseases and hypertension. One hundred and thirty research grants were awarded in the area of renal diseases, including somewhat less than 10% in studies on fluids and electrolytes, totaling about 5.0 million dollars, or 6.0% of Heart Institute research grant funds for FY 66. Another 130 projects dealt predominantly with hypertension, totaling 3.6 million dollars, or 4.3% of funds, and 83 grants for 3.0 million dollars representing 3.6% of research grant funds, devoted to studies combining renal and hypertension interests. While these reflect primarily numbers and costs of research grants, it may be noted that approximately another 10% of these figures were expended to support training grants and fellowships in the same areas of research.

In FY 66, 53 of these 343 research grants were in the areas of

artificial kidney and kidney transplantation. This includes a significant number of projects where relatively minor commitments are in the categories noted.

While the National Heart Institute conducts no organized programs in kidney disease, certain coordinated efforts can be mentioned. These take two forms of multi-disciplinary approach:

- 1) Intra-institutional, inter-departmental program projects;
and
- 2) Inter-institutional cooperative studies.

Of the 226 research grants in the etiology of kidney diseases, two are program projects dealing with renal diseases, and two other combine attacks on renal disease and hypertension. Support to these four projects amounted to \$838,000 in FY 66, averaging about \$210,000 per project. Two more program projects were supported in the renal area, directing their efforts to therapeutic implications, and costing \$905,000 or about \$450,000 per project. It may be noted also that both these latter projects deal with kidney transplantation.

Cooperative studies represent another coordinated type of attack on disease problems. The Heart Institute in FY 66 supported 36 projects in three separate cooperative studies, the total cost of which in that year was \$1,374,000. All three of these cooperative studies emphasized clinical testing of surgical or drug therapeutic measures, although not without inclusion also of a significant stress on diagnostic techniques particularly in the extensive 20-project Cooperative Study on Renovascular Hypertension. It is of interest that the two other studies, one on drug therapies and hypertension, and the other dealing with antibiotic therapy of pyelonephritis in

relation to hypertension, both are conducted entirely in PHS hospitals. A good deal of the higher cost per project in the Renovascular Hypertension Study reflects costs of hospitalization and other patient care, which are not carried by the grants to the PHS hospitals.

All together, these coordinated efforts supported by the Heart Institute amount to 42 projects, or 12% of those in the total area of kidney and hypertension research, with a support level of slightly over \$3,000,000 (see Table III), or about a quarter of the total research grant budget for these areas. Thus, while the Institute continues to emphasize support of individual, unstructured, non-directed research on hypertension and kidney disease, these more coordinated program projects and cooperative studies represent significant portions of Heart Institute support to these fields, stressing particularly many aspects of therapeutic measures.

Table III
NHI RESEARCH EXPENDITURES ON KIDNEY DISEASE

Program	1966 Expenditures
Renal Disease and Hypertension	\$1,743,000
Cooperative Studies	<u>1,374,000</u>
Total	\$3,117,000

d. Division of Research Facilities and Resources (DRFR)

Several programs are administered by DRFR which include support of research in kidney diseases.

In FY 1966, the General Clinical Research Centers program provided an estimated \$4.5 million for kidney disease research not including research in hypertension and diabetes. This program provides for the cost of remodeling and renovation necessary to establish the resource and for operating costs such as hospitalization, research nursing care and support of specialized technical personnel. Laboratory support in these centers is limited to procedures required by several different investigators. The research conducted in these centers is controlled through competition adjudicated by a local advisory committee. Since many of the investigators utilize the resource simultaneously, the award provides a flexible mechanism of bed-support which can readily adapt to the needs of many investigators at any particular time.

The Division has two other programs on which kidney research depends indirectly. The Health Research Facilities Program, budgeted at \$50 million, provides matching funds for the construction of research facilities. Any future research programs in renal diseases requiring additional space may depend heavily on this program.

A second program is the General Research Support Program, currently budgeted at \$61 million. This program assists institutions heavily involved in sponsored biomedical research to maintain a degree of flexibility in furthering their own biomedical research and research training goals. Thus this program provides backup

support for many of the categorical grants from the institutes. A summary of pertinent Division of Research Facilities and Resources expenditures is presented in Table IV.

Table IV

ESTIMATED DRFR DIRECT KIDNEY DISEASE PROGRAM EXPENDITURES

Program	1966 Expenditures
General Clinical Research Centers: Kidney Disease	\$4,500,000

2. Kidney Disease Control Branch, National Center for Chronic Disease Control

The Kidney Disease Control Program of the National Center for Chronic Disease Control has responsibilities in all areas relating to the development and demonstration of the dialysis method in communities, the training of professional and technical personnel in dialysis therapy, public and professional information and education activities, and appropriate related data collection and analysis. The Branch serves as the Public Health Service's consultative unit in dealing with official and other health agencies, hospitals, and practitioners in all aspects of the provision of dialysis services. In addition to these dialysis-related activities, the Kidney Disease Control Program conducts a broad range of preventive and educational activities in the broad kidney disease field.

Specific responsibilities in the dialysis-related areas follow.