

ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1954

NATIONAL HEART INSTITUTE

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Library, Administration Unit
National Institutes of Health
Building 10
Bethesda, Maryland 20014

U. S. National Heart Institute

Report of Program
Activities

Summary of Intramural Research Activities

Laboratory of Chemistry of Natural Products

A number of problems dealing with the isolation and study of natural materials have been pursued during the year. The research on several of these projects may be summarized as follows:

Research on Andromedotoxin, a compound found in leaves of Rhododendron maximum (the common Rhododendron of the Carolinas) continued during the year. A satisfactory method for the isolation of the substance in quantities necessary for chemical, pharmacological, and clinical work was developed. The chemical studies were largely directed to the establishment of criteria of purity and studies of derivatives. The structure of the compound is unknown, although the functional groups have been established. Pharmacological studies, in which it was found that this substance is a potent hypotensive agent acting through stimulation of the carotid sinus pressor reflex, were completed and the material was carried into clinical pharmacology studies. So far, no chemical derivatives of the original molecule have shown hypotensive action, but this area of work will be continued.

A broad study of Amaryllis alkaloids has yielded many new results. A number of previously unknown alkaloids were isolated and characterized. The structure of most of these compounds is unknown but this field is under active investigation and several proposed structures are under study. Desirable types of physiological activity are not generally associated with these compounds, but hypotensive activity has been found in a few cases. It is generally believed that a partially hydrogenated phenanthridine system is present in a number of the alkaloids, and little is known of the chemistry or physiological activity of such compounds. This project is to be continued with particular emphasis on structural determinations through degradative and synthetic studies.

The chief alkaloid of Piptadenia peregrina was found to be bufotenine (N, N-dimethylserotonin) and this established a possible connection with serotonin. Chemical studies in NIMH indicated that bufotenine has only a transient effect in humans. In cats, physiological studies indicated a relationship with lysergic acid diethylamide, as far as effects in synaptic transmission are concerned. It is not yet known whether bufotenine is a significant compound in human metabolism although it has recently been identified in human urine, but studies on both plant and animal tissue are continuing with a view to determining the nature of the indole bases which are present.

A new and interesting substance of unknown structure has been isolated from seeds of a tropical plant, *Ormosia panamensis*. This material is a potent hypotensive agent the action of which is apparently central in origin; few side effects have been noted. This observation is of considerable interest both in chemistry and in physiology. The structure of the substance is unknown, and it is difficult to isolate. The problem is further complicated by the fact that the small supplies of material available have come from a single tree. A search for additional sources of material has been instituted.

All of these projects required the support of an Isolations Section in order to provide raw materials for study, and in addition other new observations were made through the operation of an exploratory screening study. Various types of problems involving the supply of plant materials, chemical and pharmacological testing, and the development of isolation procedures arose during the year. Currently, plant collecting and some plant testing are being carried on at the Federal Agricultural Station in Puerto Rico. Isolation studies were carried on both on a large and small scale in this Laboratory and in part in cooperation with the Section on Isolation, Laboratory of Biochemistry, NIAMD.

Synthetic studies completed during the year fall largely into three groups. Most of the structural studies on natural materials required some synthetic work, and in a few cases extensive studies were undertaken. In these instances the synthetic work was correlated with degradative studies. A second field of synthetic work involved joint problems with the Laboratory of Chemical Pharmacology, NHL. The structure of a butazolidine metabolite was established by synthesis, and a number of compounds were prepared for enzyme inhibition studies. The work in intravenous anesthetics was continued. The final area of synthetic work was concerned with the development of synthetic procedures for a variety of polycyclic systems. Much of this work was also carried out in cooperation with the Laboratory of Chemical Pharmacology. The information obtained in these studies is chiefly useful in providing ways of making new compounds, but several substances with physiological activity were encountered.

Laboratory of Cellular Physiology and Metabolism - Cellular Physiology Section

The activities of the Cellular Physiology Section are concerned mainly with investigations at the cellular and subcellular level of various aspects of intermediary metabolism. Currently, research on the following biochemical topics is in progress: (1) the biosynthesis and structure of proteins, (2) the mechanism of lipoprotein hydrolysis, (3) the chemistry of "energy-rich" biosynthetic intermediates, (4) the biochemistry of muscle contraction, (5) amino acid metabolism, and (6) cholesterol oxidation. Summaries of the significant developments of these projects are given below.

(1) The Biosynthesis and Structure of Proteins. It has been proposed that cysteinyl-glycine is a recurring peptide sequence in proteins which might be derived more or less directly from glutathione. This hypothesis was tested by studying the in vitro incorporation of S^{35} -cysteine and C^{14} -glycine labeled glutathione into ovalbumin by oviduct preparations. The ovalbumin was isolated and, by means of the methods developed earlier, eleven of the fourteen theoretically possible cysteine-containing sequences were identified. Of these, only one is cysteinyl-glycine. This fact, together with results of specific radioactivity determinations of several different glycine and cysteine residues from specific sites along the ovalbumin chain, do not support any special role for glutathione in the biosynthesis of cysteinyl-glycine sequences. In other studies phosphorylated peptides from ovalbumin and pepsin have been isolated and identified. Since the sulfhydryl groups, and probably phosphate groups also, of protein molecules play important roles as specific sites of enzyme activity, these investigations on the peptide sequences adjacent to these groups provide an opportunity to examine the amino acid configuration at the "active centers" of enzymes.

Basic information of this sort is essential to the ultimate understanding of the mechanism of enzyme action and will assist also in the development of a reasonable approach to the problem of protein biosynthesis.

(2) The Mechanism of Lipoprotein Hydrolysis. Studies initiated earlier on the mechanism of the so-called "lipemia clearing" reaction have been continued. Rat heart extracts have been found to contain a specific lipoprotein lipase which catalyzes the hydrolysis of the triglyceride moiety of chylomicrons and related large lipoprotein complexes. In contrast to other lipases, this enzyme does not hydrolyze simple triglycerides; however, triglycerides are converted to enzymatically active chylomicrons by interaction with the alpha-lipoprotein fraction of normal serum. Calcium ions or a protein (viz. albumin) must be present to bind the free fatty acids released as a result of the hydrolysis. Heparin appears to be a specific activator of lipoprotein lipase and the role of this substance as a prosthetic group or coenzyme is being investigated further.

These results provide the basis of a new concept of lipid transport in which the alpha- and beta-lipoproteins and lipoprotein lipase are catalytic agents, and may have important implications in the abnormality of lipid metabolism which characterizes atherosclerosis.

(3) The Chemistry of "Energy-Rich" Biosynthetic Intermediates. Studies on the role of thiol esters as vehicles for the transfer of metabolic energy have been continued. It has been demonstrated that cell-free extracts of the bacterium Clostridium kluyveri and pigeon liver contain thiol trans-acylating enzymes which catalyze the transfer of the acyl-moiety of acyl

coenzyme A to various mercaptans. These enzyme systems provide one mechanism by which metabolic energy trapped in the form of acyl coenzyme A derivatives may be transferred, without loss, to form other thiol esters which may be more direct precursors in the synthesis of specific compounds.

(4) The Biochemistry of Muscle Contraction. Studies on the physical and chemical properties of contractile muscle have been continued. Following up the apparently anomalous observation that myosin ATP-ase may be activated by either calcium ions or the calcium binding agent ethylenediaminetetraacetic acid (EDTA), it has been shown that activation of hydrolyses by EDTA is limited to purine or pyrimidine riboside triphosphate with a 6-amino group (adenosine and cytidine triphosphates) whereas the most active substrates with calcium ion activation are the 6-hydroxy compounds (inosine and uridine triphosphates). The same enzyme appears to be responsible for hydrolysis of all the substrates. It has been found that myosin and actomyosin possess two types of sulfhydryl groups which act differently in catalyzing the hydrolysis of ATP with calcium ion as the activator. One group is essential for catalysis whereas the other exerts an inhibitory effect on hydrolysis. In the presence of EDTA the system appears to be relieved of the effect of the inhibitory group. As evidenced by studies on double refraction of flow, these sulfhydryl groups are not primarily responsible for the binding of ATP by the protein nor do they appear to be involved in maintaining the structure of the elongated particles.

(5) Amino Acid Metabolism. The enzymatic conversion of serine to glycine, formate and unidentified one-carbon derivatives by cell-free extracts of an anaerobic bacterium, Clostridium HF, has been investigated. This conversion has been shown to require DPN, orthophosphate, pyridoxal phosphate, Mn^{++} and an unidentified heat stable coenzyme. The latter coenzyme has been purified considerably and has been shown to be a folic acid derivative. Since folic acid coenzymes appear to play a key role in the metabolism of one-carbon compounds, the present enzyme system presents an excellent opportunity to explore this aspect of biochemistry in intimate detail.

Studies on the conversion of lysine to butyrate and acetate by extracts of C. HF have continued. The formation of acetate has been shown to require the presence of diphosphopyridine nucleotide, manganese and reduced lipoic acid. With certain enzyme preparations acetate and other unidentified neutral volatile compounds are produced from lysine. Identification of the latter compounds may throw light on the mechanism of butyrate synthesis from lysine. Glycine has been shown to undergo a reductive deamination to form acetate. A dithiol compound such as BAL and DPN are required for this enzymatic transformation. Preliminary tracer experiments show that the bacterial extracts catalyze the utilization of methanol for the biosynthesis of several non-volatile compounds the nature of which has not yet been determined.

(6) Cholesterol Metabolism. Studies are proceeding on the isolation of an unidentified co-factor which is required for the oxidation of the side chain of cholesterol by mouse liver mitochondria preparations. Chromatographic procedures for the partial purification of this substance from boiled extracts of calf liver have been developed and a number of the chemical properties of the substance have been determined.

Laboratory of Cellular Physiology and Metabolism - Metabolism Section

The work of the Metabolism Section over the past year has been concerned with three major areas of investigation.

One major area of research has been a continuing series of studies directed at furthering understanding of nephritis and nephrotic syndrome. On the clinical level, the possible therapeutic value of adrenal steroids is being examined. Results obtained thus far indicate that patients with nephrosis may respond with partial or complete remission after cortisone or certain new steroid compounds, metacortalone and metacortin. These cases will be followed, some on maintenance therapy over an extended period of time to determine whether the ultimate course of the disease is altered by these drugs. At the laboratory level, these investigators are studying the role of antibodies in the production of experimental nephritis. A finding of interest is that lung tissue as well as kidney contains an antigen capable of inducing the formation of nephrotoxic serum. Also of interest because of its possible implications in therapy or prevention is the observation that a soluble factor derived from the antigen is capable of neutralizing nephrotoxic antibodies. Studies directed at further characterization of this neutralizing substance are in progress.

A broad approach to the problem of lipid and lipoprotein metabolism represents a second major area of investigation. Because serum lipoproteins have been implicated in the pathogenesis of arteriosclerosis, an understanding of their normal metabolism, as well as changes in diseased states, is of importance. A series of studies on the interrelationships of serum lipoproteins have been undertaken. It has been found that the phospholipid moieties are rapidly exchangeable between the different ultracentrifugal classes of lipoproteins. Preliminary studies with carbon-14 labeled lipoproteins suggest that the protein moiety of one class of lipoprotein can form the protein nucleus of a different ultracentrifugal class of lipoprotein. These observations require confirmation and are being repeated both in vivo and in vitro. Immunochemical studies have revealed that there is at least an antigenic relationship between the protein found in chylomicrons and that in Sf 3-8 beta lipoproteins. These studies also demonstrated an immunochemical inhomogeneity of ultracentrifugally and electrophoretically pure Sf 3-8 beta lipoproteins. Whether this apparent inhomogeneity is due to differences in the proteins or due to differences in the lipid composition of these lipoproteins is not clear.

A new technique for analysis of human serum lipoproteins has been developed. This method gives much of the information normally obtained by the use of analytical ultracentrifugation but requires only the use of the Spinco preparative ultracentrifuge, an instrument much more widely available. This method consists essentially of the repeated centrifugation of the lipoproteins at progressively increasing salt densities in order to resolve the different protein classes. A series of heparin-like materials have been tested for their ability to induce clearing of lipemic serum. A large series of electronegative compounds (sulfuric acid derivatives and phosphate derivatives) have been found to mimic the action of heparin. Since other work in the laboratory has indicated that heparin is an essential coenzyme for the lipoprotein lipase of heart muscle, it appears that these unphysiological compounds are capable of replacing heparin as a co-factor.

The metabolism of free fatty acids in plasma is under investigation. It has been observed that during the action of clearing factor the fatty acids split from lipoproteins become bound to serum albumin, changing its electrophoretic mobility quite markedly. An intriguing question, as yet unanswered, is that of whether the fatty acids so released are transferred into metabolizing cells directly or indirectly through the mediation of serum albumin. Studies of the fate of the free fatty acids in plasma show a uniform rise after a fatty meal and a uniform fall after ingestion of glucose. Preliminary studies with C^{14} labeled fatty acids indicate a very rapid turnover. A convenient electro-metric titration method for determination of fatty acid content of plasma has been developed.

The mechanism of cholesterol degradation by cell-free liver preparations is being studied. Two degradation products have been isolated and partially characterized. One is an ester of cholesterol and the second is an as yet unidentified compound more highly polar than the cholesterol itself. The observation that a cell-free preparation can carry out the esterification of cholesterol is a valuable one and may make it possible to determine what factors govern this process.

At the clinical level studies of the lipoprotein pattern in disease states are being continued. Both the chemical and ultracentrifugal patterns are being determined in conditions such as idiopathic hyperlipemia, xanthoma tendinosum, xanthoma tuberosum, biliary cirrhosis and coronary atherosclerosis. The effects of long-range administration of heparin and of estinyl are being examined. While there appears to be a lowering of serum cholesterol and a well recognized alteration in the serum lipoprotein pattern following estrogen administration, it is too early to evaluate the therapeutic value of these agents.

A third major area of investigation is in the general field of protein structure and metabolism. Previous studies have shown that the entrance of labeled amino acids into proteins occurs at different rates at different sites in the molecule. One possible explanation for this observation is that there are reversible reactions involved in protein synthesis. A series of in vitro studies on protein degradation by liver and kidney slices under physiological conditions has been undertaken to obtain evidence for or against this hypothesis. It has been found that dinitrophenol at concentrations that inhibit protein synthesis also inhibits protein degradation. In addition it has been found that amino acid analogues at concentrations that inhibit protein synthesis also inhibit protein degradation. Control studies show that these effects are not related to the oxidative metabolism of the cell. They suggest that there may be an intermediate relation between the synthetic and degradative pathways of protein metabolism. This is being further investigated in cell-free preparations.

A special case of protein degradation, namely the degradation of insulin by mammalian liver enzyme, is being investigated. It has been established that the loss of biological activity of insulin in the presence of liver slices or liver homogenate is due to proteolytic cleavage of the molecule. Specific inhibitors for the purified enzyme system are being sought because of the obvious potential clinical interest in such inhibitors.

Laboratory of Technical Development

The efforts of this laboratory have been directed to the development of new instruments and methods in support of the program of other Heart Institute laboratories and toward the development of new technics for the furtherance of research.

An ultraviolet photofluorimeter has been developed in cooperation with the Laboratory of Chemical Pharmacology which promises to greatly widen the scope of such instruments and make possible analytical methods of very high sensitivity for the determination of a number of compounds of biological interest. The instrument provides a means of activating fluorescence with ultraviolet light of any desired wave length and detection of the light emitted throughout the ultraviolet and visible range. It has been applied to the identification and quantitative determination of serotonin and related indole derivatives and it should be possible to apply the instrument to the measurement of normal amounts of epinephrine in blood. A commercial instrument patterned after the device designed in this laboratory will soon be available.

An apparatus for the ultramicro determination of sodium and potassium is under development. The instrument, it is hoped, will make possible the analysis of amounts of material (10^{-10} to 10^{-12} mols) such as might be obtained on micropuncture of individual tubules - or possibly even on the contents of single cells. The principle is that of gaseous discharge in vacuo, ionization and emission of material sealed in a quartz tube being induced by a high intensity microwave field produced in a specially designed wave guide cavity. The sensitivity of the method has been established; the quantitative aspects are being investigated.

In studies basic to the use of deuterium for the determination of the water content of biological systems, the exchangeable hydrogen of various proteins and amino acids has been determined. In addition study of detailed adsorption-desorption isotherms has yielded information concerning the "binding" of water by various proteins.

Apparatus has been developed for the detailed analysis of events in the processes of freezing and drying. The physics of these processes is under study for application to methods of fixation with particular reference to the preparation of materials for electron microscopy. Rates of cooling are being related to the size and number of ice crystals in order that artefacts of this origin can be avoided.

An instrument has been devised which rapidly provides a Fourier analysis of any desired biological wave form. The frequency spectrum obtained defines the response characteristics required of an instrument which is to record the wave form. Biological curves of various types and sources have been investigated.

A device which provides a means of obtaining cardiac x-rays at selected phases of the cardiac cycle has been constructed. This provides information concerning movements and changes in the heart size at specific points in the contraction of the heart.

Laboratory of Chemical Pharmacology

The program of the Laboratory of Chemical Pharmacology has been combined with that of the Laboratory of Physiology and Pharmacology of the Autonomic Nervous System and is concerned with many aspects of therapeutic agents including their effects on enzyme systems in cells, on organ systems, and on the complete organism including man. Some of the accomplishments of the past year may be summarized as follows:

Serotonin and Tranquillizing Agents. Serotonin, a substance discovered in the body fairly recently, is generally regarded as a new hormone but its role has not been clearly defined. It constricts blood vessels by a peripheral action and consequently has been thought to be involved in the etiology of hypertension though this possibility is no longer seriously considered. It has been thought to be present in platelets and its local constrictive action on its release in bleeding has been considered as an important aid in the stoppage of bleeding. This laboratory has chemically identified serotonin in platelets and is studying its concentration in the various bleeding diseases. The hormone is present in the brain in relatively large amounts. It is antagonized in a number of in vitro preparations by lysergic acid diethylamide (LSD), a substance which produces a schizophrenia-like state in man. From these observations the tenuous though exciting theory has been suggested that serotonin plays an important part in brain function, a function which is antagonized by LSD. If true this would present a chemical basis for neuro-psychological disorders.

Studies in this laboratory have tended to substantiate this point of view. Chlorpromazine and reserpine, two drugs used in hypertension, are also used in psychotic states as tranquillizing agents, both producing a type of sedation not seen with ordinary sedatives. It has been shown in this laboratory that these compounds also potentiate the action of central nervous system (CNS) depressants without alteration of the rate of their biotransformation. Serotonin has also been shown to have a "sedative" action and to produce similar potentiation. The action of all three compounds is blocked by LSD. This work not only shows for the first time an antagonism between LSD and serotonin in the total organism and at a CNS level but suggests that reserpine and chlorpromazine act on the CNS through liberation of serotonin. Direct support for this hypothesis is given by experiments in which reserpine administered to dogs results in a many-fold increase in the urinary excretion of 5-hydroxyindoleacetic acid, a major metabolite of serotonin. This work makes it seem highly likely that serotonin is important in normal brain function.

The synthesis of this substance by the body has been studied. It is formed from the amino acid tryptophan. The enzyme systems have been purified, making it possible to study inhibitors which may block serotonin formation. If inhibitors can be found that are active in vivo, then the role of serotonin might be more clearly appraised by the study of serotoninless animals.

Detoxication of Drugs. The length of time a drug exerts its effects is usually limited by the rate of its "detoxication" to products with little or no activity. It has always been a mystery how the body is able to inactivate

a drug it has never "seen" before, for most body enzymes possess considerable specificity in order to protect the biochemical reactions they control.

A group of investigators in this laboratory found that the majority of drugs are metabolized by extraordinarily non-specific enzyme systems in the little-studied submicroscopic particles of liver (microsomes). They are all blocked by certain inhibitors (SKF 525-A, Marsilid, etc.) and require both oxygen and reduced TPN. Biochemically this represents a strange type of hydrogen transport, and preliminary evidence indicates that TPNH reacts with a flavoprotein and oxygen to yield H_2O_2 , which in the presence of the required non-specific peroxidase can split ethers, oxidize ring side chains, dealkylate alkylamines, oxidize alcohols, hydroxylate rings, etc. It is believed that this group of microsomal enzyme systems is not essential to normal physiologic processes, but rather performs the role of a non-specific defense against foreign compounds entering the body via the alimentary tract.

Species differences which make it so difficult to transfer the results of animal experiments directly to man have been shown for a number of drugs to be a result of species variation in activity of this particular microsomal enzyme system.

Drug-Screening. A drug-screening program has been initiated and is working in close collaboration with the clinical pharmacology group and with industry. Some of the results obtained with Andromedotoxin and with other plant materials are referred to elsewhere in this report.

A number of drugs have been screened for effectiveness in the treatment of abnormal heart rhythms and one of these, an antimalarial, SN2157, seems good enough to try in man. MC4112, a procaine amide analogue obtained from industry, has been shown both in animals and in man to be inferior to procaine amide.

A new compound, G-25671, a butazolidin analogue, which is less effective than butazolidin as an anti-rheumatic agent but does not cause retention of sodium and water at therapeutic doses, has been developed through the efforts of this group. In addition it seems to have an extraordinary effect in increasing the excretion of uric acid. For these reasons the compound should be very useful in the treatment of chronic gout provided it does not cause side effects on long-term administration. The drug is presently under test in several clinics throughout the country. In further studies of butazolidin, two metabolic products have been isolated from urine and identified. Preliminary experiments indicate that at least one of these exerts a pronounced anti-rheumatic effect and is presently under intensive study.

Laboratory of Cardiovascular Hemodynamics

This laboratory has, for practical purposes, been operating for only a part of the last year. The personnel and program are new and the necessity of organizing and setting up techniques and procedures has occupied a major part of the six months during which the group has been established. Nevertheless progress has been made in several lines of investigation.

As a possible means of treating aortic stenosis a procedure has been devised for short-circuiting the aortic valve. This involves the use of a lucite prosthesis containing a ball valve connecting the apex of the left ventricle to the descending thoracic aorta. This rather novel and daring procedure has been applied in dogs and these animals, with the ascending aorta totally ligated, appear healthy and vigorous. A number of technical problems remain to be overcome before the operation could be applied in man. Chief among these is the avoidance of crannies in which clot can form at the junction of vessel and prosthesis. An additional problem has become apparent in some of the dogs in that a hemolytic anemia has developed, apparently as a result of damage to red cells from the impact of the ball on the valve seat. Because of the greater fragility of dog red cells as compared to human cells, this may not be a serious problem in man, but the question is being investigated by studies of mechanical fragility of dog and human red cells and by study of patients in whom valve prostheses have been inserted for the treatment of aortic insufficiency.

The circulatory effects of breathing against high levels (50-60 mm Hg) of positive pressure have been under investigation. The problem is one which is pertinent in high altitude aviation where loss of cockpit pressurization can leave the flyer at a pressure level too low to supply adequate oxygen tensions even with the use of 100 per cent oxygen. It is then necessary to supply oxygen at positive pressures. Applied to animals this leads to circulatory standstill in a few minutes by a mechanism which has been shown in this laboratory to be analogous to cardiac tamponade. It has been found that an adequate circulation can be maintained for fairly long periods by the administration of sympathomimetic amines.

Studies of the maintenance and modification of blood vessel tone have been initiated. Apparatus and techniques have been devised for the study of isolated blood vessel segments and studies of pressure-volume relationships have been initiated.

Laboratory of Kidney and Electrolyte Metabolism

The normal distribution of electrolytes in the body and the maintenance of normal body composition with respect to fluid and electrolytes are effected by specific transport mechanisms which move electrolytes across living membranes. The major efforts of this laboratory have been directed at an understanding of the way these mechanisms operate normally and of the manner in which they are deranged in cardiac failure and other disorders. These studies fall into three groups - 1) the study of the mechanisms which effect the movement of electrolytes across isolated membranes, 2) the investigation of processes involved in the handling of fluid and electrolyte by the kidney, and 3) the study of experimental heart failure and the disorders of electrolyte metabolism it involves.

Detailed study of electrolyte transport mechanisms can most effectively be carried out in situations in which isolated systems can be examined in detail. Two such systems - that which transports potassium into red cells and that which effects secretion of chloride by the isolated stomach mucosa - have been under investigation. The role of various oxidative and glycolytic systems in the uptake of potassium by red blood cells has been studied and the effect of various substrates and inhibitors has been determined. These investigations have not yet reached the point where definitive conclusions can be drawn. The isolated frog gastric mucosa has been shown to transport chloride by a process effectively involving exchange with bicarbonate ions. This is the only system in which active movement of chloride has been definitively demonstrated.

A substance present in normal blood which maintains the normal contractility of heart muscle, apparently by regulating the uptake of potassium by heart muscle fibres, has been under study in collaboration with the Laboratory of Chemical Pharmacology. This material which has an action very similar to that of digitalis may be normally secreted by the body and play a role in the regulation of heart function. It is present in minute amounts in blood and liver, from which sources it has been purified to a considerable degree. Methods have been worked out by which it should be possible to isolate amounts sufficient for chemical characterization and further studies of its physiologic role and pharmacologic effect.

The mechanism by which the kidney regulates acid-base balance and effects a part of the reabsorption of sodium by replacing sodium with ammonium ions in the urine has been considerably clarified by recent work in this laboratory. It has been shown that the only active transport mechanism involved is that which renders the urine acid by exchanging hydrogen ions for sodium ions. The ammonia enters the urine by diffusion in the uncharged state and becomes ammonium ion by combination with hydrogen ion. The

rate at which ammonia is excreted is a function of the length of tubule over which the urine is acid and of the rate at which ammonia can be produced from precursors through the activity of various enzymes, notably glutaminase, the activity of which has been shown to vary with the state of acid-base balance in rats. Studies aimed at determining the immediate stimulus to this enzymic adaptation are being pursued further.

Studies of renal transport mechanisms have now reached a point where more direct observation could yield invaluable information on the processes involved. Accordingly, plans have been made and the necessary techniques are being developed for a new series of micropuncture studies involving puncture and perfusion of individual kidney tubules in the amphibian, *Necturus*. It is hoped that these efforts will reach the point of definitive studies within the next year.

Future studies of kidney function as well as investigations of the distribution of fluid and electrolytes in tissues may be greatly facilitated by a method developed in the last year for labelling the standard reference substance, inulin, with radioactive carbon. This not only greatly simplifies the procedure necessary for physiologic studies using inulin but completely eliminates the problem of blanks which has made analysis of many tissues virtually impossible.

Studies of the mechanisms involved in experimental heart failure have been continued. A reliable method has been evolved for the production of experimental right-sided heart failure by progressive constriction of the pulmonary artery. Studies of hemodynamic events have been carried out and the response to digitalis preparations studied in detail. The role of the adrenal in the excessive retention of salt and water has been evaluated and the results, confirming previous studies in animals with ascites due to constriction of the inferior vena cava, indicate that increased activity of adrenal hormones is involved in the disorder of electrolyte and fluid metabolism.

Clinic of Gerontology

The aim of the program of this group is a definition of the physiologic consequences of aging. Toward this end studies in three general fields have been conducted: 1) cardiovascular, 2) renal function, and 3) metabolism and endocrinology. Extensive psychologic studies are planned, but have not yet been initiated.

In the cardiovascular field, studies have been conducted on wave propagation in human arteries in vivo. The analysis of pressure curves at a number of points along the aorta indicates a highly complicated propagation

system with various harmonics transmitted at different velocities and with the velocity of a given frequency varying from location to location. The relationship between diastolic and pulse pressure on one hand and mean arterial pressure on the other has been shown to vary with age reflecting a more prolonged systolic rise in the older individual. An agewise study of cardiac output has been completed. The average reduction in tissue perfusion with age has been found to exceed the average reduction in various indices of tissue mass - such as total body water, O₂ consumption or CO₂ elimination. These studies indicate that the reduction of the circulation with age is not secondary to a decline in cell mass or cell activity, but may well be the primary event in this process.

Studies have been directed at determining whether there are detectable changes in measurable enzyme activity in the aging kidney. To date, succinoxidase activity has been measured and found to be unchanged in aged rats (over 2 yrs.) as compared with the activity in kidneys of young animals. A decrease of the activity of this enzyme system in the heart muscle of the older animals was, however, detected and it was possible to show that this was not attributable to a reduction in the cellularity of the tissue.

A series of glucose tolerance and glucose-insulin tests has been completed. A significant decrease with age has been found in the rate of disappearance of administered glucose from the blood. Thus the old individual does not respond to insulin as effectively as does the young. These results may be interpreted in terms of diminished metabolic activity in the older subjects.

Clinic of General Medicine and Experimental Therapeutics

The activities of the Clinical Endocrinology Section have been directed largely at evaluation of the role of adrenal steroids in states associated with the formation of edema, and at determining the physiologic role of aldosterone and factors controlling its secretion. A method for the bioassay of adrenal salt-retaining steroids has been developed using the dog as the experimental animal. The assay method has adequate sensitivity and the distinct advantage of a type of control which makes it possible to exclude non-specific effects reducing the excretion of sodium. A colony of adrenalectomized dogs has been established for use in the assay procedure and a satisfactory level of productivity has been attained. Using this method, extracts of urine from edematous subjects have been examined and shown to contain amounts of aldosterone in excess of normal. The rate of excretion of aldosterone (rate of secretion?) has been found to be relatively unaffected by ACTH and to persist in hypopituitarism and the data to date suggest that the volume of the extracellular fluids may be the determining factor.

Two new steroids, metacortandracin and metacortandralone, have been studied for their metabolic effects and therapeutic value in various disease states. The studies show that these compounds have the anti-inflammatory activity of cortisone but are without salt-retaining activity.

The Section on Experimental Therapeutics has instituted studies in several fields. Major efforts have been devoted to setting up a unit for examining agents for blood pressure reducing activity. The mode of action and value of andromedotoxin have been evaluated. When administered by intravenous infusion, it is capable of reducing the blood pressure sharply. The reduction is maintained for periods of 1 to 3 hours and the effects can be reversed by the administration of atropine. Other routes of administration are currently under study but do not appear promising. As in animals, the effects in man are similar to those of Veratrum alkaloids and its usefulness will probably be similarly limited to acute situations such as hypertensive encephalopathy and toxemias of pregnancy.

In conjunction with the Laboratory of Chemical Pharmacology, studies of anti-arrhythmic agents have been initiated. The first substance evaluated, MC4112, an analogue of procaine amide, has been found to be less effective than the parent compound. Other anti-arrhythmic drugs are currently undergoing preliminary study before trial in man.

The role of naturally-occurring pressor substances in the control of blood pressure is being studied. A method of measuring catechol amines in blood has been developed. The amine oxidase mechanism is being studied in relation to serotonin, tyramine and other related substances.

The Section on Cardiodynamics has been concerned with the characteristics of ventricular ejection under varying degrees of diastolic filling. It has been shown that the volume of ventricular ejection is only partly related to the filling time. The factor of "recovery time" of myocardial fibres has been largely discounted since hemodynamic factors have been shown to be of greater importance.

Clinic of Surgery

The main projects of the Clinic of Surgery have been concerned with the physiologic studies in valvular disease and the evaluation of methods for demonstrating intracardiac shunt. Left atrial puncture has been performed in more than 75 patients. Patterns characteristic of mitral stenosis and insufficiency have been evolved. Additional data in aortic valve disease are

being compiled. A technique has been devised for left ventricular catheterization through the bronchial needle and this procedure has been performed successfully in 12 patients. This has made it possible to determine pre-operatively the pressure gradient across the mitral valve. It is hoped that this will aid greatly in selecting patients for mitral commissurotomy and in evaluating the physiologic benefit which has accrued from the operative procedure.

Major activities in the experimental surgical laboratory have been concerned with the problems of open cardiac surgery. In the hypothermic animal with circulatory occlusion, infiltration of the sino-auricular (SA) node by local anesthesia has been effective in preventing ventricular fibrillation in all of the animals studied, whereas fibrillation occurs in more than 90 per cent of control animals subjected to the same procedure. The SA node block has recently been employed in the treatment of 2 patients with interatrial septal defects which were successfully closed by the use of hypothermia and open heart surgery. Other projects in the laboratory include investigation concerning the role of digitalis in hypothermia, the development of an improved aortic valve, attempts at perfection of an extracorporeal pump-oxygenator or artificial heart and evaluation of plastic tubes for replacement of aortic segments.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-1C
SERIAL NO.
6. Renal Function and Water Excretion in Diabetes Insipidus
PROJECT TITLE
7. Dr. Jack Orloff, Dr. Hans Keitel, Dr. Mackenzie Walser (and Dr. F. C.
PRINCIPAL INVESTIGATOR(S) Bartter, Clinic of Gen. Med. & Exper.
Therap.)
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of the project is to investigate the mechanism involved in the production of dilute urines.

Methods Employed: The methods employed in this study have been standard clearance techniques and standard metabolic balance procedures.

Patient Material: (1954 calendar year)

		<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions:	Children male	1	150
	Children female	1	150
Outpatient:	Number of patients	1	
	Number of visits	1	

9. PROJECT DESCRIPTION (continued)

Major Findings: The free water clearance has been determined in a number of acute experiments during which various manipulations have been performed, and the findings to date have been consistent with the hypothesis that the urine is diluted by the extraction of sodium salts and that the free water clearance may be the equivalent of some specific moiety of the sodium reabsorbed. Studies of the relationship between urine flow and dietary solute intake have been carried out and it has been found that the correlation between urine flow and solute excretion, under these conditions, was relatively poor since the free water clearance appeared to increase progressively on a low solute intake.

Significance to HEART Research: These studies should provide information concerning the nature of the mechanism for the excretion of water and the mechanism for the reabsorption of sodium.

Proposed Course of Project: The studies are to be continued and the effect of various manipulations and various drugs on the excretion of water and electrolyte will be determined.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-1C
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 16,000	3	3	6	1.17	1.33	2.50	150
FY 1956	18,000	3	3	6	1.67	1.33	3.00	300

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

Clinic of General Medicine and Experimental Therapeutics,
NHI - Dr. F. C. Bartter -- Serial No. NHI-50C

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-1C
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-2C
SERIAL NO.

6. Renal Function in Sickle Cell Anemia and Factors Related to Crises in Sickle Cell Anemia
PROJECT TITLE

7. Dr. Hans Keitel
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this study are 1) to determine the nature of the disturbance which leads to inability of sickle cell anemia patients to elaborate a concentrated urine; and 2) to attempt to evaluate metabolic factors which may be involved in the precipitation of sickle cell crises.

Methods Employed: Standard methods for evaluating renal function and multiple transfusion of packed red cells.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	2	200
Children female	1	250
Outpatient: Number of patients	20	
Number of visits	40	

9. PROJECT DESCRIPTION (continued)

Major Findings: Patients with sickle cell anemia who have been studied have been found to have renal function equal to or greater than the average normal in all respects except for an inability to elaborate a concentrated urine. In several patients this defect has been shown to be reversible when a patient's own sickle red cells had disappeared completely after multiple transfusions. The concentrating ability of individuals with sickle cell trait has been found to be normal. The acquisition of the concentrating defect in early life is being evaluated. Studies to determine whether the sickle cell crises might be precipitated by metabolic acidosis secondary to acute infection have lent no support to this hypothesis.

Significance to HEART Research: These studies may contribute to an understanding of the nature of the mechanism for diluting and concentrating the urine.

Proposed Course of Project: Further studies of the development of the concentrating defect and its reversal by transfusion are planned.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-2C
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 7,000	1	1	2	.50	.50	1.00	650
FY 1956	7,000	1	1	2	.50	.50	1.00	325

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-2C
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-3C
SERIAL NO.
6. The Relationship Between Urine pH and Excretion of Weak Electrolytes
PROJECT TITLE
7. Dr. Jack Orloff and Dr. Robert W. Berliner
PRINCIPAL INVESTIGATOR(S)
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To determine the mechanism whereby certain weak acids and bases, particularly ammonia, are excreted by the kidney.

Methods Employed: The methods employed have in general been standard clearance techniques and standard chemical methods.

The underlying principle has been to use the excretion of certain exogenous weak bases as an internal standard for the differentiation between the physical factors affecting the movement of ammonia into the urine and biochemical factors involved in the production of ammonia by kidney cells.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	1	235

9. PROJECT DESCRIPTION (continued)

Major Findings: It has been shown that the movement of weak bases into the urine can be explained on the basis of an equilibrium between cell contents and tubular fluid with respect to the unionized base in a system where the membrane is almost impermeable to ions. The excretion of quinine and certain acridine derivatives parallels that of ammonia in the dog when only changes in pH and flow are involved. At low pH movement of ammonia into the urine appears to be diffusion limited in both dog and man. In man the excretion of quinine is affected to only a minimal extent by a variation in urine pH and it does not appear likely that quinine can be used in man to measure the physical factors involved in weak base excretion.

Significance to HEART Research: The excretion of ammonia is an important aspect of the renal reabsorption of sodium. An understanding of its mechanism is important to the clarification of the processes which are disturbed in cardiac failure.

Proposed Course of Project: Studies of the effect of infusion of potassium salts and of the administration of ammonia precursors will be extended in the dog and it is anticipated that the observations in man will be continued.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-3C
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 9,000	2	3	5	.33	.84	1.17	118
FY 1956	9,000	2	3	5	.33	.84	1.17	118

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-3C
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT
DURING CALENDAR YEAR 1954:

Berliner, R. W.: The Kidney. Annual Review of Physiology, 16,
269-304, 1954.

Berliner, Robert W., Kennedy, Thomas J., Jr., and Orloff, Jack:
Factors Affecting the Transport of Potassium and Hydrogen Ions by
the Renal Tubules. Arch. int. Pharmacodyn., XCVII, 299-312,
1954.

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-4
SERIAL NO.
6. Anion Transport Across the Gastric Mucosa
PROJECT TITLE
7. Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR(S)
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To elucidate the dynamics of anion transport and to determine the nature of the anion transport system.

Methods Employed: The methods used in general have followed the principles set forth by Ussing, i. e., the measurement of unidirectional ion fluxes across isolated membranes in relation to the electrical potential with regulation of the electrical potential at desired levels.

Major Findings: Thiocyanate fluxes have been measured at 0 and at 60 mV. The nutrient to secretory flux at 0 mV is about 1.5 times that in the opposite direction, indicating that thiocyanate is actively transported in the same direction as chloride. The rate of thiocyanate transfer in either direction is not influenced by replacing the major anion, chloride, by nitrate. Comparing thiocyanate and chloride in the same concentration with nitrate the predominant anion, both anion fluxes are reversed at 60 mV. Chloride has relatively greater fluxes, suggesting a greater affinity of chloride for the carrier transfer and marked reduction of carrier back transfer at low concentrations of either ion. It has been possible to show that the turnover across the nutrient surface of the epithelium is considerably faster than across the secretory surface for both thiocyanate and chloride.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: The frog gastric mucosa presents a unique opportunity for the study of a more or less isolated anion transport system which can serve as a guide and model for anion transport systems elsewhere in the body.

Proposed Course of Project: Observations on the carbonic acid bicarbonate system in relation to chloride transport will be extended. Study of the flux of nitrate and its relationship to the movement of chloride will be carried out.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-4
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 11,000	1	2	3	.33	1.00	1.33	-
FY 1956	11,000	1	2	3	.33	1.00	1.33	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-4
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT
DURING CALENDAR YEAR 1954:

Hogben, C. A. M.: Active transport of chloride by isolated frog gastric epithelium: Origin of the gastric mucosal potential. Amer. Jour. Physiol. (In Press)

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NIH-5C
SERIAL NO.

6. A Comparison of the Clearance of Total Inulin, Yeast-stable Inulin
and Alkali-stable Inulin
PROJECT TITLE

7. Dr. Mackenzie Walser, Dr. Douglas Davidson, and Dr. Jack Orloff
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine whether the clearance of alkali-stable inulin is the same as that of alkali-labile inulin and to evaluate the validity of the resorcinol method for the determination of inulin.

Methods Employed: A new method for the determination of inulin using alkali to destroy saccharides and diphenylamine for color development has been devised. Otherwise standard chemical procedures and clearance techniques have been used.

Patient Material: No patients have been admitted specifically for this project. Patients under study for other reasons have been examined in this project.

Major Findings: To date the clearances of alkali-stable and yeast-stable inulin have been uniformly identical within the errors of the methods. Total inulin determined by the resorcinol method has departed widely in both directions from the clearances of the other materials. It is apparent that the errors which arise in determination of plasma inulin using the resorcinol method are probably due to variability in the very considerable blank.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: If these findings are confirmed, they will lead to a simplification of the measurement of glomerular filtration, a procedure central to a number of physiologic studies.

Proposed Course of Project: The observations in both patients and dogs will be extended.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-5C
SERIAL NO.

11. _____
BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 4,500	3	1	4	.83	-	.83	-
FY 1956	4,500	3	1	4	.83	-	.83	-

12. _____
BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-5C
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE

2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHI-6
SERIAL NO.

6. Metabolism of Urea in Man
PROJECT TITLE

7. Dr. Mackenzie Walser
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This study is intended to determine whether conversion to creatinine accounts for the extrarenal clearance of urea in normal subjects.

Methods Employed: Determination of the isotope abundance in nitrogen after ingestion of N¹⁵ urea.

Major Findings: Methods for the isolation of creatinine and its conversion to creatine have been worked out and a sample of creatine has been prepared from creatinine from a subject who had ingested N¹⁵. The results were inconclusive and the experiment is to be repeated.

Significance to HEART Research: If significant amounts of urea are converted to creatinine, a new metabolic pathway will have been discovered. This may have fundamental biochemical significance.

Proposed Course of Project: This project will be completed when a sample of creatinine currently being isolated has been analyzed.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-6
SERIAL NO.

11. _____
BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 2,000	1	-	1	0	0	0	-
FY 1956	2,000	1	-	1	0	0	0	-

12. _____
BUDGET ACTIVITY:

- RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIE Program Activities
Honors, Awards, and Publications Sheet

15. NHI-6
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE

2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NIH-7
SERIAL NO.

6. The Exchange of CO₂ and Hydrogen Ions Between Extra-cellular Fluids and Cells In Vivo
PROJECT TITLE

7. Dr. Mackenzie Walser and Dr. Jack Orloff
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To estimate the changes in cell pH and CO₂ content in response to acute alterations in extracellular pH, CO₂ tension and bicarbonate concentration.

Methods Employed: An arterial infusion of acid or base is given into one hind limb of the dog and rapid collections of venous blood from the same limb are made over a short interval. The concentration-time curves of pH, CO₂, blue dye, and various electrolytes are determined.

Major Findings: These studies have only recently been initiated and technical problems are being worked out.

Significance to HEART Research: Current estimates of intracellular electrolyte composition are inadequate for most purposes and any procedure which will throw light on this problem would have far-reaching significance for the study of the electrolyte metabolism of tissues.

Proposed Course of Project: Results to date do not appear too promising and unless major technical problems can be worked out the project will be discontinued.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-7
SERIAL NO.

11. _____
BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 2,000	1	1	2	.33	-	.33	-
FY 1956	2,000	1	1	2	.33	-	.33	-

12. _____
BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIN Program Activities
Honors, Awards, and Publications Sheet

15. NHI-7
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHL-8
SERIAL NO.

6. Ammonia Excretion in the Rat
PROJECT TITLE

7. Dr. Edward Leonard and Dr. Jack Orloff
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To correlate excretion of ammonia with the production of ammonia by kidney slices and kidney homogenates.

Methods Employed: Excretion of ammonia in intact rats subject to various experimental manipulations has been studied using the technique of infusion and urine collection devised in this laboratory. The production of ammonia with glutamine by kidney slices has been studied by the procedure of Davies and Yudkin and the production of ammonia for glutamine by kidney homogenates has been determined.

Major Findings: Major findings may be summarized by saying that in the rat the rate of excretion of ammonia is only minimally affected by changes in urine pH. It appears in general to be most closely related to changes in over-all acid-base balance. There is a general correlation of the rate of ammonia excretion with the glutaminase activity of the kidney but the departures from this direct relationship, particularly in acute acidosis, are sufficient to indicate the operation of other important factors.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: The excretion of ammonia is an important aspect of the renal reabsorption of sodium. An understanding of its mechanism is important to the clarification of the processes which are disturbed in cardiac failure.

Proposed Course of Project: This project has been completed.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-8
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 7,000	2	2	4	1.00	.33	1.33	-
FY 1956	-	-	-	-	-	-	-	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NHI-8
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT
DURING CALENDAR YEAR 1954:

Leonard, Edward, and Orloff, Jack: The regulation of ammonia excretion in the rat. Amer. Jour. Physiol. (in Press)

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHI-9
SERIAL NO.

6. Mechanisms of Electrolyte Excretion in the Chicken
PROJECT TITLE

7. Dr. Douglas Davidson, Dr. Jack Orloff, and Dr. Robert W. Berliner
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objective of this project is to utilize the unique anatomic arrangement of the chicken kidney to further the elucidation of the mechanisms involved in electrolyte transport by the kidney tubules.

Methods Employed: The technique in use has been the administration of various electrolyte solutions into the vein of one leg and the collection of samples from the ureters of the individual kidneys.

Major Findings: The administration of potassium salts on one side results in the rapid excretion of potassium, particularly from the side of administration, an elevation in urine pH and increased excretion of sodium and chloride on the same side. Infusion of ammonium chloride causes an elevation of excretion of ammonia on the same side. Excretion of inulin by the two kidneys is essentially identical and independent of the route of administration.

Significance to HEART Research: It is hoped that these studies will help to clarify the nature of electrolyte transport mechanisms of the kidney.

Proposed Course of Project: These studies which have only recently been initiated will be extended.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-9
SERIAL NO.

11. _____
BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 10,000	3	3	6	.83	1.17	2.00	-
FY 1956	10,000	3	3	6	.83	1.17	2.00	-

12. _____
BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-9
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-10
SERIAL NO.
6. Measurement of Gastric Blood Flow
PROJECT TITLE
7. Dr. C. Adrian M. Hogben
PRINCIPAL INVESTIGATOR(S)
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To devise a method for measuring blood flow to the gastric mucosa in the intact individual.

Methods Employed: The principle of the method is based on the observation that the rate of appearance of certain basic chemical compounds in the gastric juice appears to be limited by the blood flow. This suggests the possibility that the measurement of the rate of appearance in gastric juice in relation to the concentration in the blood might serve as a measure of the blood flow. Studies have been done on dogs with Heidenhain pouches and other acute experiments on operated dogs.

Major Findings: Methods have been devised for the determination of low concentrations of neutral red in whole blood and these have been applied to the measurement of gastric mucosal blood flow in Heidenhain pouch dogs. Values of the order of 6 ml./min./kilo of body weight have been found. The extragastric disposition of this dye has also been determined.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: This project represents the application to a practical purpose of an observation in a totally unrelated field, namely a study of the disposition of drugs in the body.

Proposed Course of Project: The studies with the secretion of neutral red will be extended and the validity of the dye clearance as a measure of blood flow will be examined by the use of another substance the uptake of which can be shown to limit blood flow.

Analysis of NIH Program Activities

Budget Data Sheet

10. NMI-10
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 5,000	1	2	3	.33	1.00	1.33	-
FY 1956	7,000	2	2	4	.33	1.00	1.33	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

This project is being carried out in collaboration with Dr. L. M. Hershenson of NIAMD.

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-10
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-11
SERIAL NO.
6. Hydrodynamic Aspects of Biological Membranes
PROJECT TITLE
7. Dr. C. Adrian M. Hogben (and Dr. Harold Morowitz, Lab. of Technical
PRINCIPAL INVESTIGATOR(S) Development)
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The objectives of this project are to formulate a satisfactory analysis of the relationship among ion fluxes and osmotic and hydrodynamic flow.

Methods Employed: An apparatus has been developed consisting of a chamber with a single aperture covered by the membrane under study. The pressure within the chamber can be determined by a non-displacement strain gauge manometer and volume displacement can be followed by a precision plunger driven into the chamber.

Major Findings: The efforts to date have been directed to the perfection of apparatus and techniques.

Significance to HEART Research: Estimate of solvent drag effect upon ion flow is a prerequisite for interpretation of many aspects of active transport and passive diffusion.

Proposed Course of Project: When the technique has been satisfactorily worked out, the apparatus will be applied to the study of movement of solvent across natural membranes.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-11
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 12,000	1	2	3	.33	1.50	1.83	-
FY 1956	13,000	1	2	3	.33	1.50	1.83	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

Laboratory of Technical Development, NHI (Dr. Harold Morowitz),
Serial No. NHI-41

14. None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NHI-11
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHI-12
SERIAL NO.

6. Cation Transport Across Cell Membranes
PROJECT TITLE

7. Dr. Daniel C. Tosteson
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To identify the physicochemical processes responsible for transport of potassium and sodium across cell membranes.

Methods Employed: The methods employed have been the measurement of the movements of radioactive cation into and out of red blood cells and a study of the effect of various inhibitors and variation in concentration of substrate and various ions.

Major Findings: Further study of the blood cells of patients with sickle cell anemia has confirmed the hypothesis that sickling accelerates non-free diffusion processes which transport sodium out of and potassium into the cell and opens the pathway for the free diffusion of both ions. Studies of normal human red cells tagged with sodium²⁴ by pre-incubation in radioactive plasma have shown that the specific activity in the cells incubated in non-radioactive medium remains 20 per cent above the equilibrium value after 48 hours. Potassium transport in duck red cells has been studied by varying medium composition, substrate concentration, by incubating/¹⁵Oxygen and nitrogen, and by studying the effect of various metabolic inhibitors. The results of these studies have not yet reached the point where it is possible to identify with certainty the nature of the processes necessary for potassium transport. Further studies of the effect of butanol on transport impermeability of human red cells have been carried out.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: These studies will yield fundamental information concerning the nature of transport mechanisms which are basic to other systems.

Proposed Course of Project: An attempt to identify specific chemical reactions involved in potassium transport will be continued. Further definition of inhibitor effects, measurement of the relation between magnesium and potassium transport, and the characterization of sodium transport are planned. Measurements will be made of the kinetics of chloride penetration into human red cells with the use of a flow tube. Measurements will be made of the affinity constants of various nucleotide polyphosphates for sodium and potassium by potential measurements across cation selective membranes.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-12
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 18,000	1	3	4	1	3	4	-
FY 1956	18,000	1	3	4	1	3	4	-

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-12
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE

2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHI-13
SERIAL NO.

6. Cardiovascular and Renal Hemodynamic Function and Electrolyte and Water
Metabolism in Experimental States Associated with Edema and Ascites
PROJECT TITLE

7. Dr. James O. Davis
PRINCIPAL INVESTIGATOR(S)

8. Dr. David S. Howell, Dr. Robert Hyatt, and Dr. M. Jay Goodkind
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the role of various hemodynamic and endocrine factors which may contribute to the retention of salt and water in the formation of edema.

Methods Employed: Edema and ascites have been produced by constriction of the inferior vena cava and cardiac failure with ascites and edema have been produced by constriction of the pulmonary artery. Attempts to produce left-sided heart failure by the induction of aortic insufficiency and constriction of the aorta are currently in progress. Electrolyte excretion has been evaluated by standard metabolic balance techniques, renal function has been evaluated by the measurement of PAH and creatinine clearances, and pressures in various parts of the cardiovascular system have been measured by catheterization techniques and optical recording.

9. PROJECT DESCRIPTION (continued)

Major Findings: 1) Dogs with constriction of the inferior vena cava. It has been confirmed that the pituitary is not essential to the maintenance of ascites in dogs with constriction of the inferior vena cava. In two instances where diuresis has followed hypophysectomy, reconstruction of the inferior vena cava has resulted in a reaccumulation of fluid. The effect of the pituitary in maintaining the elevated level of venous pressure can be reproduced by the administration of growth hormone. In adrenalectomized dogs with constricted vena cava, it has been found that the response to mercurial diuretics is not influenced by doses of DCA between 1 and 25 mg/day.

2) Cardiac failure produced by constriction of the pulmonary artery. A number of animals have been adrenalectomized in order to evaluate the role of the adrenals in the retention of fluid and electrolyte in this condition. In general, it has been found that rather large doses of DCA are required to reproduce the salt retention observed in the animals in which adrenals were intact. The data suggest that the amount of hormone required may be less in this preparation than in the dog with constricted inferior vena cava. The effect of anemia in dogs with constriction of the pulmonary artery has been studied and it appears that cardiac failure can be precipitated in the presence of a constriction not in itself sufficient to lead to fluid retention.

3) Others. The effect of hypophysectomy on cardiovascular hemodynamic function in the dog has been evaluated. A striking decrease in cardiac output has been found to result.

Significance to HEART Research: These studies represent an experimental approach to the study of factors involved in cardiac failure and the evaluation of the role therein of various hemodynamic and hormonal factors.

Proposed Course of Project: In addition to further study of the findings described above, assays for sodium-retaining activity will be carried out on urine from dogs with thoracic caval constriction and with cardiac failure due to pulmonary artery constriction. It is planned to carry out the study of ventricular function curves in dogs with cardiac failure secondary to pulmonary artery constriction.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-13
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$48,000	3	5	8	3	5	8	-
FY 1956	48,000	3	5	8	3	5	8	-

12. BUDGET ACTIVITY:

- RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NIH-13
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT
DURING CALENDAR YEAR 1954:

Davis, James O., Howell, David S., Laqueur, Gert L., and Peirce, E. Converse II.: Renal hemodynamic function, electrolyte metabolism and water exchange in adrenalectomized-hypophysectomized dogs. *Am. J. Physiol.*, 176, 411, March 1954.

Davis, James O., Howell, David S., and Hyatt, Robert E.: Effect of chronic pitressin administration on electrolyte excretion in normal dogs and in dogs with experimental ascites. *Endocrinology*, 55, 409, 1954.

Howell, David S. and Davis, James O.: Relationship of Na retention to K excretion by the kidney during administration of desoxycorticosterone acetate to dogs. *Am. J. Physiol.* (In Press)

Davis, James O., Hyatt, Robert E., and Howell, David S.: Right-sided congestive heart failure in dogs produced by controlled progressive constriction of the pulmonary artery. *Circulation Research*. (In Press)

Davis, James O., Howell, David S., and Hyatt, Robert E.: Effect of acute and chronic digoxin administration in dogs with right-sided congestive heart failure produced by pulmonary artery constriction. *Circulation Research*. (In Press)

Howell, David S., Davis, James O., and Laqueur, Gert L.: Effect of hypophysectomy on electrolyte excretion in dogs with ascites produced by thoracic inferior vena cava constriction. *Circulation Research*. (In Press)

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-14
SERIAL NO.

6. Biological Assay and Isolation of a Digitalis-like Substance from Blood Serum and Tissues
PROJECT TITLE

7. Dr. Stephen Hajdu
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Previous studies on the frog heart suggested the presence of a digitalis-like substance in blood serum. The purpose of this research is to isolate this substance, to characterize it chemically and to determine its role in the control of the contraction of the heart.

Methods Employed: An assay for digitalis-like activity has been developed using the staircase phenomenon of the frog heart. A new procedure using pigeon right ventricle is currently under study. The methods of isolation have involved extraction with organic solvents and chromatography.

Major Findings: The concentration of the active material has been studied in various tissues in different animals and averages not higher than 1 mg/kilo of tissue. The highest concentration so far detected was in the adrenal medulla and none of the material could be detected in the adrenal cortex. This suggests that the substance is produced by the chromaffine system as is the only other known digitalis-like substance in animal tissue, the cardiotonic steroids found in toad venom. In accord with the belief that the production is derived from

9. PROJECT DESCRIPTION (continued)

the chromaffine system is the finding of a high concentration of the active principle in the urine of a patient with intestinal carcinoid. Preliminary difficulties in the isolation of the material have been overcome and it is believed that a procedure has been worked out which will make possible the isolation of larger amounts of material for chemical characterization.

Significance to HEART Research: The identification and study of a substance which may play a fundamental role in regulating heart muscle contraction is obviously of the greatest importance to our understanding of the function of the heart.

Proposed Course of Project: Isolation of sufficient material to make possible chemical identification is planned. Studies of the possible physiologic role of the material in the regulation of the heart under normal and abnormal conditions will be undertaken.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-14
SERIAL NO.

11. _____
BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 16,000	1	2	3	1.00	1.50	2.50	-
FY 1956	16,000	1	2	3	1.00	1.50	2.50	-

12. _____
BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. _____
IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

Laboratory of Chemical Pharmacology, NHI, Serial No. NHI-143

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-14
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH
5. NHI-15
SERIAL NO.
6. Studies on the Function of Single Nephrons in Necturus
PROJECT TITLE
7. Dr. Thomas J. Kennedy, Jr.
PRINCIPAL INVESTIGATOR(S)
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This project is directed toward the amplification of knowledge concerning the alteration of glomerular urine in its transit through the nephron with particular regard to the evaluation of the processes involved in electrolyte transport.

Methods Employed: The method for the collection of samples from the individual tubules is to be that developed by Richards and his collaborators, and the technique for the perfusion of individual nephrons will also be that of the aforementioned group. Chemical methods will be ultra-micro adaptations of standard procedures and entirely new methods worked out in collaboration with the Laboratory of Technical Development.

Major Findings: Efforts to date have been devoted to the development and adaptation of methods to the minute samples which will be available. Harrison's method for determination of inulin has been modified for performance in capillary tubes and for final colorimetry in the Beckman spectrophotometer. Equipment has been obtained and set up and preliminary trials of the technique of puncturing tubules has been undertaken.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: The abnormal handling of electrolytes by the kidney is a central feature of cardiac failure and our capacity to analyze the nature of the defect is limited by our understanding of the normal mechanism.

Proposed Course of Project: Further development of methods and techniques will be required before proceeding to definitive studies of the movement of electrolytes into and out of the tubular lumen in relation to such factors as concentration gradients, pH and electrical potential.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-15
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 6,000	1	0	1	1.00	-	1.00	-
FY 1956	8,000	1	1	2	1.00	.33	1.33	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-15
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHI-16
SERIAL NO.

6. Investigation of Diffusion Processes Across Ion
Selective Membranes
PROJECT TITLE

7. Dr. Melvin Gottlieb
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The investigation of the kinetics of ion transfer across membranes bearing fixed charges and the correlation of the kinetics with electrical potential, resistance and ionic selectivity.

Methods Employed: Ionic flux of labelled radioactive ions is measured across collodion membranes containing ion exchange groups introduced by the addition of appropriate reagents. The electrical potential between solutions of different ionic composition on two sides of the membrane and the resistance of the membrane to alternating currents are measured by standard techniques.

Major Findings: The diffusion of potassium chloride from solutions of concentrations from .001 to 1.0 molar across membranes of varying electrical resistance has been studied. Diffusion rates across the highest resistance membranes were found to vary by a factor of 3 over a 1000-fold range of solution concentration, while with those of lowest resistance the rates varied by a factor of 25. Diffusion rates measured radiochemically agreed well with those measured by the exchange of potassium for ammonium ion so that ammonium ion can be used as a tracer of potassium in membranes of this type. Observed diffusion rates agree approximately with those calculated from the resistance.

9. PROJECT DESCRIPTION (continued)

Significance to HEART Research: The full development of an understanding of the behavior of inert charged membranes is of considerable importance to the interpretation of ion movements across the very much more complicated biological membranes.

Proposed Course of Project: The study of ion exchange across permselective membranes will be extended to movement of anions in cation impermeable membranes. The exchange of one ion against another of different species in the presence and absence of concentration gradients will be attempted.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-16
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 6,000	1	0	1	1	0	1	-
FY 1956	6,000	1	0	1	1	0	1	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-16
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Kidney and Electrolyte Metabolism
LABORATORY OR BRANCH

5. NHI-17
SERIAL NO.

6. C¹⁴-Labelled Inulin As a Tracer for Inulin
PROJECT TITLE

7. Dr. Ernest Cotlove
PRINCIPAL INVESTIGATOR(S)

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The object of this project is to develop a tracer for inulin which will 1) simplify the analytical procedure for the measurement of inulin clearance, and 2) permit the analysis of inulin at very low concentration in body fluid and tissue by elimination of blanks which interfere with the colorimetric methods.

Methods Employed: The physiologic procedures which have been employed are standard procedures for the evaluation of renal function, and the method for injection of materials and collection of samples in the rat are those which have been worked out in this laboratory.

Major Findings: The preparation of C¹⁴ inulin has been studied. The material which is now being used is prepared by cyanohydrin synthesis which introduces a carboxyl group. Attempts at enzymatic incorporation of C¹⁴-labelled fructose units into non-radioactive inulin have been partially successful but the method does not seem sufficiently promising to warrant further study. Methods for the preparation of plasma, urine and tissue samples for analysis of C¹⁴ inulin have been worked out and the reliability and correction factors have been determined. The recovery in the urine of C¹⁴-labelled inulin in man has

9. PROJECT DESCRIPTION (continued)

been found to average 100 per cent in 6 patients and to average 98 per cent in a group of rats. The clearance of C^{14} inulin was the same as chemical inulin in 2 patients and at tracer levels in the rat yielded the same average inulin clearance as that obtained using larger amounts of non-radioactive inulin. The kinetics of the excretion of C^{14} inulin in the urine has been evaluated. Perfusion of isolated intestine for two hours resulted in no loss of inulin from the gastrointestinal tract.

Significance to HEART Research: The distribution of electrolytes in tissue is of considerable importance to our understanding of factors influencing cellular activity such as muscular contraction. To evaluate the distribution of electrolytes in tissue it is necessary to be able to measure the volume of extracellular fluid. The use of non-radioactive inulin for this purpose presents difficulties because of chromogenic blanks and analytical errors. The C^{14} inulin should go a long way toward obviating these difficulties. In addition, the availability of C^{14} inulin for the measurement of glomerular filtration should greatly simplify and possibly increase the accuracy of this procedure.

Proposed Course of Project: Further study of the recovery of radioactivity in the urine in man is necessary before a dose may be chosen which will render negligible the radiation hazard. When this has been accomplished, further comparison of clearance of radioactivity with clearance of chemical inulin will be desirable. When these problems have been worked out, application of the method to the purpose for which it is intended will be undertaken.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-17
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$ 16,000	1	2	3	1	2	3	-
FY 1956	16,000	1	2	3	1	2	3	-

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-17
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT
DURING CALENDAR YEAR 1954:

E. Cotlove: Mechanism and extent of distribution of inulin and
sucrose in chloride space of tissues. Amer. Jour. Physiol., 176,
396, 1954.

17. None

Project Description Sheet

1. HEART
INSTITUTE

2. SURGERY
LABORATORY

5. NHI - 18C
SERIAL NO.

6. Determination of Left Ventricular Pressure in the Intact, Unanesthetized Patient.
PROJECT TITLE

7. Andrew G. Morrow, M. D.
PRINCIPAL INVESTIGATOR(S)

8. J. Alex Haller, Jr., M. D., Donald L. Fry, M. D.
(OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION:

Objectives: Develop a satisfactory method for the measurement of left ventricular pressure in the intact patient.

Methods Employed: Needle puncture of the left atrium is an established method for entrance into this chamber. It has been found possible to pass a small catheter through the left atrial needle and into the left ventricle. The entire procedure is carried out bronchoscopically.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	10	20
Adult females	10	20
Children	0	0
Outpatient: Number of Patients	0	

Major Findings: Successful entry into the ventricle has been effective in 8 of 16 patients. Difficulty has been encountered with assembling of a recording system of sufficient sensitivity.

Significance to HEART Research: Reliable ventricular pressures in the intact patient opens an almost unlimited field of physiologic study in all types of heart disease. In particular one can calculate precisely the pressure gradients across the mitral and aortic valves. This should enable better selection of patients for operation and more accurate assay of operative results.

Proposed Course of Project: Efforts will be continued to perfect the details of the technique and obtain data in as many patients as possible.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 18C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED	POSITIONS			MAN YEARS			PATIENT
	EXPENDITURES	PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	DAYS
FY 1955	11,500	2	2	4	.67	.83	1.50	25
FY 1956	11,500	2	2	4	.67	.83	1.50	50

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NIH-19C
SERIAL NO.

16. None

17. None

Project Description Sheet

1. HEART
INSTITUTE

2. SURGERY
LABORATORY OR BRANCH

5. NHI - 19C
SERIAL NO.

6. Determination and Evaluation of Left Atrial Pressure in Congenital and
PROJECT TITLE

Acquired Heart Disease.

7. Andrew G. Morrow, M. D.
PRINCIPAL INVESTIGATOR(S)

8. J. Alex Haller, Jr., M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the left atrial pressure in the intact, un-anesthetized patient and to correlate the tracings with surgically proven heart disease.

Methods Employed: A bronchoscope is passed into the left bronchus and a needle inserted through the bronchus into the left atrium. By means of a suitable recording system pressures and pulse contours in the left atrium are recorded. The procedure has been carried out without incidence in 75 patients with various types of heart disease and in 10 individuals with normal hearts bronchoscoped for other reasons.

Patient Material: (1954 calendar year)

	No.	Average Stay Days
Admissions: Adult males	14	20
Adult females	2	20
Children	0	0
Outpatient: Number of patients	0	

Major Findings: A definite correlation between the left atrial pressure curve and the presence or absence of mitral stenosis and insufficiency can be made. These data are being assembled for publication. Determinations have been performed in congenital and many other types of acquired heart disease but not in sufficient numbers for compilation.

Significance to HEART Research: Left sided pressures have heretofore been unobtainable and calculation of intracardiac flow have required estimation made only on clinical grounds. Numerous physiologic observations can now be made utilizing this technique.

Proposed Course of Project: Left atrial pressures will be obtained in virtually all patients presented with congenital and acquired heart disease. As sufficient data in each group are collected they will be compiled and analyzed.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 19C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	18,500	2	3	5	.67	1.83	2.50	100
FY 1956	18,500	2	3	5	.67	1.83	2.50	150

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None

P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 19C
SERIAL NO.

16. None

17. None

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 20C
SERIAL NO.
6. Ventricular Fibrillation in Hypothermia
PROJECT TITLE
7. Leo R. Radigan, M. D.
PRINCIPAL INVESTIGATOR(S)
8. Thomas A. Lombardo, M. D.
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: Determine the mechanics of and means of prevention of ventricular fibrillation in the hypothermic animal or patient.

Methods Employed: A standard operation has been evolved consisting of circulatory occlusion for 8 minutes at 28°C and right ventriculotomy. In this situation all control animals have had ventricular fibrillation. Various measures may be tested for their effectiveness in preventing this phenomenon.

Major Findings: Block of the S.A. node with local anesthesia will prevent fibrillation in all instances. The mechanism of this prevention is not known.

Significance to Heart Research: Prevention of fibrillation is of extreme importance in that hypothermia is currently the most satisfactory means of open heart surgery. If it can always be prevented in patients, a large obstacle to the use of this technique will have been removed.

Proposed Course of Project: Further experiments to elucidate the mechanism of the S.A. node block are being carried out. Dogs with surgically produced heart block are being tested. Sympathetic and parasympathetic denervation are being tested for their effect.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 20C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	14,300	2	1	3	.83	1.00	1.83	25
FY 1956	17,942	3	1	4	1.83	1.00	2.83	156

12. BUDGET ACTIVITY:

RESEARCH X

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 20C
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE

2. SURGERY
LABORATORY OR BRANCH

5. NHI - 21C
SERIAL NO.

6. Myocardial Failure in Experimental Hypothermia
PROJECT TITLE

7. Thomas A. Lombardo, M. D.
PRINCIPAL INVESTIGATOR(S)

8. Leo R. Radigan, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To establish that heart failure is a cause of death in experimental hypothermia and to determine the best means of prevention and treatment.

Methods Employed: A test operation consists of circulatory occlusion for 8 minutes at 28°C and right ventriculotomy has been used. Venous, arterial and ventricular pressures have been measured before and after circulatory occlusion.

Major Findings: All animals who had the test operation alone were found to demonstrate the physiologic criteria for heart failure. When rapidly acting digitalis compounds were given, heart failure was prevented and survival was much greater than in controls.

Significance to Heart Research: Causes of death in hypothermia have never been fully elucidated. The demonstration of heart failure plays an important part. This will enable patients to be properly treated before and after reduction in temperature. This should make the technique safer and thus more widely applicable.

Proposed Course of Project: Further observations on the development of heart failure and the effect of agents other than digitalis are under investigation

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 21C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	12,400	2	1	3	.83	1.00	1.83	25
FY 1956	15,800	3	1	4	1.83	1.00	2.83	50

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION —
REVIEW & APPROVAL — TECHNICAL ASSISTANCE —

13. None

14. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI - 21C
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 22C
SERIAL NUMBER
6. Digitalis Tolerance in Experimental Hypothermia
PROJECT TITLE
7. Thomas A. Lombardo, M. D.
PRINCIPAL INVESTIGATOR(S)
8. OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To determine the safe and effective dosage of digitalis for the hypothermic heart.

Methods Employed: Dogs have been titrated to the end point of ventricular tachycardia with rapidly acting digitalis compounds. These dogs are later cooled to 25°C and again titrated.

Major Findings: The hypothermic heart is much more sensitive to the action of digitalis than is the heart at normal temperature. Respiratory rate and temperature have an effect on the susceptibility of the cold heart to digitalis.

Significance to Heart Research: Most patients operated upon for heart disease are receiving digitalis. If the patient is to undergo hypothermia, it is important to know the optimal dosage as too much of the compound may induce ventricular fibrillation.

Proposed Course of Project: Digitalis will be continued as outlined above and various digitalis and allied compounds will be surveyed.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 22C
 SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	5,000	1	1	2	.33	1.00	1.33	10
FY 1956	5,000	1	1	2	.33	1.00	1.33	20

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION —
 REVIEW & APPROVAL — TECHNICAL ASSISTANCE —

13. None

14. None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 22C
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 23
SERIAL NO.

6. The Experimental Production of Physiologically Competent Valves in the
PROJECT TITLE Descending Aorta of Dogs.

7. Ian K. R. McMillan, M. B.
PRINCIPAL INVESTIGATOR(S)

8. Joseph Roshe, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To produce a competent aortic valve in dogs with aortic insufficiency.

Methods Employed: A valve constructed entirely of nylon cloth has been devised. This valve is inserted into the thoracic aorta by means of direct suture. Moderate hypothermia is used to permit prolonged periods of aortic occlusion.

Major Findings: The valve is found to function effectively and blocks the physiologic defects of surgically induced aortic insufficiency.

Significance to Heart Research: The present surgical treatment of aortic insufficiency is unsatisfactory. It is hoped that this valve may prove useful in clinical treatment of patients with aortic valve lesions.

Proposed Course of Project: Many more animals must be studied. The wearing characteristics of the valve must be determined and the long term survival determined.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-23
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	18,000	2	2	4	1.50	2.00	3.50	0
FY 1956	21,400	2	3	5	1.50	3.00	4.50	0

12. BUDGET ACTIVITY:

RESEARCH	<u>X</u>	ADMINISTRATION	---
REVIEW & APPROVAL	---	TECHNICAL ASSISTANCE	---

13. None

14. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI - 23
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 24
SERIAL NO.

6. Experimental Pulmonary Stenosis
PROJECT TITLE

7. Jerome Harold Kay, M. D.
PRINCIPAL INVESTIGATOR(S)

8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To produce pulmonary stenosis which is comparable to that seen in patients. The methods of surgical attack on the lesion may then be satisfactorily studied.

Methods Employed: The cusps of the pulmonary valve are sutured together under direct vision using hypothermia for circulatory occlusion.

Major Findings: A number of animals have survived the operative procedure but have not as yet been studied physiologically.

Significance to Heart Research: Several operative methods for the treatment of pulmonary stenosis are presently available. The choice of method is now largely arbitrary and not based on experimental evidence. These studies should indicate the best treatment of the lesion seen clinically.

Proposed Course of Project: Additional animals must be subjected to operation followed by physiologic study and evaluation of treatment.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 24
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	10,000	1	1	2	.33	1.00	1.33	0
FY 1956	10,000	1	1	2	.33	1.00	1.33	0

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION —
REVIEW & APPROVAL — TECHNICAL ASSISTANCE —

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 24
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Experimental Production of Pulmonary Stenosis: Physiological and Pathological Study. Archives of Surgery, 69:651-657, Nov., 1954.

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 25
SERIAL NO.

6. Experimental Pulmonary Insufficiency
PROJECT TITLE

7. Jerome Harold Kay, M. D.
PRINCIPAL INVESTIGATOR(S)

8. J. Alex Haller, Jr., M. D. & Robert A. Gaertner, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To produce gross pulmonary insufficiency in dogs and study the physiologic sequelae of the lesion.

Methods Employed: One or more cusps in the pulmonary valve are excised under direct vision using hypothermia and circulatory occlusion. The surviving animals are then subjected to physiologic study.

Major Findings: In the few animals studied elevation of right sided pressure and heart failure has occurred.

Significance to Heart Research: It is commonly believed that insufficiency of the pulmonary valve as a clinical lesion is entirely harmless. This is important in selecting the method of treatment of pulmonary stenosis. The studies indicate that competence of the valve must be a necessary feature of any operation upon it.

Proposed Course of Project: Additional animals will be subjected to the operation and study outlined.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 25
 SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	14,400	2	1	3	.83	1.00	1.83	0
FY 1956	14,400	2	1	3	.83	1.00	1.83	0

12. BUDGET ACTIVITY:

RESEARCH	<u>X</u>	ADMINISTRATION	—
REVIEW & APPROVAL	—	TECHNICAL ASSISTANCE	—

13. None

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 25
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR
YEAR 1954:

Experimental Production of Pulmonary Insufficiency: Physiological and
Pathological Study, Arch. of Surg., 69:646-651, November, 1954.

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 26
SERIAL NO.

6. Experimental Use of a Pump Oxygenator
PROJECT TITLE

7. Jerome Harold Kay, M. D.
PRINCIPAL INVESTIGATOR(S)

8. Robert A. Gaertner, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To develop satisfactory extracorporeal circulation which will permit prolonged periods of circulatory occlusion for open-cardiac surgery.

Methods Employed: A dispersion oxygenator and finger pump have been used in preliminary studies. This unit has been found unsatisfactory because of damage to blood protein. Perfusion of the brain and heart with fresh oxygenated blood with slight hypothermia has been found practical.

Major Findings: Many problems concerned with the method have been worked out but a satisfactory system has not yet been evolved.

Proposed Course of Project: Further study of various types of oxygenators is under way. Perfusion rates are being determined and the proposed usefulness of hypothermia as an adjunct is under study.

Significance to Heart Research: Open-heart surgery is necessary for the treatment of a large number of congenital and acquired lesions. The usefulness of hypothermia is limited and eventually a satisfactory artificial circulation will be necessary.

Analysis of NIH Program Activities

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 26
SERIAL NO.

6. Experimental Use of a Pump Oxygenator
PROJECT TITLE

7. Jerome Harold Kay, M. D.
PRINCIPAL INVESTIGATOR(S)

8. Robert A. Gaertner, M. D.
OTHER INVESTIGATORS

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Major Findings: Many problems concerned with the method have been worked out but a satisfactory system has not yet been evolved.

Proposed Course of Project: Further study of various types of oxygenators is under way. Perfusion rates are being determined and the proposed usefulness of hypothermia as an adjunct is under study.

Significance to Heart Research: Open-heart surgery is necessary for the treatment of a large number of congenital and acquired lesions. The usefulness of hypothermia is limited and eventually a satisfactory artificial circulation will be necessary.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 26
 SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	14,500	2	1	3	.83	1.00	1.83	0
FY 1956	14,500	2	1	3	.83	1.00	1.83	0

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION —
 REVIEW & APPROVAL — TECHNICAL ASSISTANCE —

13. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI - 26
SERIAL NO.

16. None

17. None

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 27
SERIAL NO.

6. Experimental Mitral Insufficiency
PROJECT TITLE

7. J. Alex Haller, M. D.
PRINCIPAL INVESTIGATOR(S)

8. Andrew G. Morrow, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To produce mitral insufficiency in dogs and study the physiologic changes in chronic preparations.

Methods Employed: Mitral insufficiency is produced by transventricular severance of the chordae tendineae.

Major Findings: The degree of insufficiency compatible with chronic survival has been determined and the operative technique perfected. Left atrial pressure is elevated and pulse curves characteristic of the lesion have been recorded.

Significance to Heart Research: Pure mitral insufficiency is rarely seen in patients and little opportunity is offered for the clinical study of the hemodynamic changes associated with it. The pulse contours obtained in these animals are an aid in determining the left atrial tracings obtained in patients.

Proposed Course of Project: Animals will be subjected to left and right sided cardiac catheterization and also angiocardiography.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 27
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	7,500	2	1	3	.67	.33	1.00	0
FY 1956	7,500	2	1	3	.67	.33	1.00	0

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION —
REVIEW & APPROVAL — TECHNICAL ASSISTANCE —

13. None

14. None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI - 27
SERIAL NO.

16. None

17. None

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 28
SERIAL NO.

6. Experimental Production and Study of Chronic Aortic Regurgitation in Dogs
PROJECT TITLE

7. Joseph Roshe, M. D.
PRINCIPAL INVESTIGATOR(S)

8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To produce chronic aortic insufficiency in experimental animals.

Methods Employed: Portions of the aortic cusps are excised by a specially developed instrument introduced into the aortic wall.

Major Findings: The degree of insufficiency compatible with chronic survival has been determined. This can be correlated with the size of the defect produced. Aortic catheterizations have shown remarkable pulse gradients in various portions of the arterial system.

Significance to Heart Research: Physiologic study of patients with aortic valve disease is sometimes hazardous. Experimental preparation described offers an unusual opportunity for study of the hemodynamics of aortic insufficiency. It also offers a test preparation for determining the usefulness of surgical treatment.

Proposed Course of Project: Further animals will be prepared and the physiologic studies continued.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 28
 SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	11,500	1	1	2	.50	1.00	1.50	0
FY 1956	11,500	1	1	2	.50	1.00	1.50	0

12. BUDGET ACTIVITY:

RESEARCH	<u>X</u>	ADMINISTRATION	---
REVIEW & APPROVAL	---	TECHNICAL ASSISTANCE	---

13. None

14. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI - 28
SERIAL NO.

16. None

17. None

Project Description Sheet

1. HEART
INSTITUTE
2. SURGERY
LABORATORY OR BRANCH
5. NHI - 29
SERIAL NO.
6. Experimental Myocardial Infarction
PROJECT TITLE
7. Thomas N. P. Johns, M. D.
PRINCIPAL INVESTIGATOR(S)
8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study the effect of myocardial infarction in small animals.
Methods Employed: Myocardial infarction is produced in rats by suture ligation of the left coronary artery. The animals are studied for exercise tolerance.
Major Findings: Large numbers of these animals with infarcts appear to have exercise tolerance no different from that of unoperative controls.
Significance to Heart Research: Rodents are not subject to ventricular fibrillation and thus the direct application of this work is probably not possible. The method, however, enables large numbers of inbred animals with infarcts to be rapidly and easily prepared.
Proposed Course of Project: Further study of exercise tolerance in myocardial infarction is being carried out.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 29
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	6,058	1	0	1	1.00	0	1.00	
FY 1956	6,058	1	0	1	1.00	0	1.00	

12. BUDGET ACTIVITY:

RESEARCH X ADMINISTRATION —
REVIEW & APPROVAL — TECHNICAL ASSISTANCE —

13. None

14. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI - 29
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR
YEAR 1954:

Experimental Myocardial Infarction. I. A Method of Coronary Occlusion
in Small Animals. Annals of Surgery.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-30
SERIAL NO.

6. Cardio-Roentgen Actuator
PROJECT TITLE

7. Frank W. Noble - Bert R. Boone - Harold T. Dodge
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide a means for obtaining simultaneous frontal and lateral radiographs of the cardiac shadow at known time relationships to the cardiac cycle. From these radiographs the heart size at any time in the cardiac cycle can be obtained. The progress of the heart size of a patient under treatment can be followed more accurately.

Methods Employed: The electrocardiograph R wave is used to initiate a calibrated time delay network which in turn actuates the roentgenoscope at the end of the delay interval. Since the mechanical events of the heart are well correlated with the electrocardiographic wave, this system provides a means of photographing the heart at any phase in its cycle. A photocell sensitive to x-ray is attached to the electrocardiograph in such a way as to produce a mark on the electrocardiogram indicating the exact time of exposure of the film.

Major Findings: The apparatus has been found to perform as required and is now available for use in the x-ray department.

Significance to HEART Research: Radiographs of the heart can now be made at any desired phase of the cardiac cycle.

Proposed course of project: The project as proposed is completed.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-30
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$9,200	2	2	4	.83	.34	1.17	
FY 1956	0	0	0	0	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-30
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

TITLE: A Cardiac-Roentgen Actuator: An Instrument for Actuating the Roentgenoscope in end-systole or end-diastole of the Heart Action.

AUTHORS: Frank W. Noble, Bert R. Boone, Harold T. Dodge, Armand Brodeur.
Journal of Laboratory and Clinical Investigation - March, 1954.

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-31
SERIAL NO.

6. Function Generator and Fourier Analyzer
PROJECT TITLE

7. Frank W. Noble, Robert L. Bowman, Bert R. Boone
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To provide means for easily and quickly obtaining the Fourier Analysis of any biological wave form, and for checking this analysis by synthesis. Required frequency bandwidth of recording apparatus can be determined from the results of the analysis.

Methods Employed: Electronic apparatus has been designed and built which will convert a biological curve into an electric wave of suitable frequency for connection into a commercial wave analyzer. The measurement of phase is accomplished by generation of a harmonic series of sine and cosine waves of the proper combination such that when their sum is subtracted from the biological wave a null for all frequencies is produced. Thus a true six term Fourier analysis is obtained.

Major Findings: A six term Fourier Analysis can be obtained in a time of minutes instead of the days required by the conventional graphical-schedule method. The analysis can be checked by reconstruction of the curve from the analysis and comparing it with the original.

Significance to HEART Research: Fourier analysis of accurate biological waveforms allows the specification of the required dynamic properties of a recording device. Since the analysis is unique, it provides a sensitive method of cataloguing waveforms. Information concerning the wave propagation properties of arteries may be available from such analyses.

Proposed Course of Project: The instrument is just being completed. Its stability, accuracy, and ease of operation will be studied using waveforms of known frequency content. Upon completion of these studies, pressure curves obtained from chambers of the heart by Drs. Morrow and Fry will be analyzed.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-31
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$10,200	3	3	6	.83	.67	1.50	
FY 1956	0	0	0	0	0	0	0	

12. _____
BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-31
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH
5. NHI-32
SERIAL NO.
6. A Magnetically Modulated Converter
PROJECT TITLE
7. Frank W. Noble and John L. Stephenson
PRINCIPAL INVESTIGATOR(S)
8. _____
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To develop a "d. c. amplifier" having high gain, high input impedance, low noise and excellent baseline stability.

Methods Employed: The method employed will be that of magnetically modulating the electron beam in a special gated beam tube. Small signals applied to the grid of the tube will appear at its output as an amplitude modulated wave suitable for amplification in ordinary fashion to high level. Following amplification, the signal will be demodulated and used to drive a recording device.

Major Findings: Preliminary models of this device have been built using commercially available tubes. The sensitivity of the converter can be greatly increased by employing a special tube with higher gain and greater sensitivity to the modulating field. The results to date indicate that the objectives of the project can be met by further work.

Significance to HEART Research: An amplifier of this type can be used to advantage wherever the true d. c. amplification, low noise, and stability are of value. Examples are the use for amplifying thermocouples, thermistors, muscle potentials, skin potentials, after potentials, etc.

Proposed course of Project: A special vacuum tube is being designed and will be constructed in the near future. Subsequent tests will indicate design changes required for improved performance.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-32
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,600	2	2	4	0	.67	.67	
FY 1956	11,500	3	3	6	.50	1.00	1.50	

12. _____
BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

R.P.C.-3

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-32
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-33
SERIAL NO.

6. Development of Methods for Measurement of Dielectric Dispersion for Solutions of Biologically Active Molecules
PROJECT TITLE

7. Frank W. Noble and Harold J. Morowitz
PRINCIPAL INVESTIGATOR(S)

8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop and evaluate instruments which will bring the measurement of dielectric constant into the range of the biological investigator.

Methods Employed: The present method consists of the use of a commercial Schering bridge and signal generator connected into a special detector circuit to measure the capacitance of a test cell in the range 400 KC - 50 MC.

Major Findings: Using the present measuring system, we have been able to measure the capacitance of a test cell containing dilute saline solutions at several frequencies through the range of the equipment.

Significance to HEART Research: Little biological use has been made of the measurement of dielectric constant owing to the technical difficulty of measurement and certain problems in interpreting the results. This technique will aid materially in the study of the physical and chemical properties of proteins.

Proposed course of Project: A good electrolytic cell has been designed and the materials have been ordered. The project may be discontinued after January 21 because of the departure of Dr. Morowitz.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-33
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,500	2	1	3	.33	.34	.67	
FY 1956	0	0	0	0	0	0	0	

12. _____
BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-33
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-34
SERIAL NO.

6. General Instrument Development
PROJECT TITLE

7. Frank W. Noble and John L. Stephenson
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To facilitate and implement the instrumentation problems of this and other laboratories of the Heart Institute. Typical examples are as follows:

1. In cooperation with Dr. John L. Stephenson, a direct coupled preamplifier was built to allow longer term oscillographic records to be made of the rapid freezing of materials. An investigation was made of both series - balanced and parallel-balanced d. c. amplifiers in an effort to reduce drift.

2. In cooperation with Dr. Donald Fry, a magnetically driven pressure generator was built to test the dynamic performance of blood pressure manometers. A special beat oscillator was built having a continuous range of zero to 150 cycles per second and an output voltage proportional to tuning shaft position. This test system automatically plots the amplitude-frequency characteristic on a cathode ray oscilloscope.

3. In cooperation with Dr. Donald Fry, a device was built for adding a 1500 cycle per second triangular wave to the output of a Polyviso Recorder. This enables the record taken by an oscilloscope and camera system to be analyzed on the Fourier analyzer. Frequency response requirements of respiratory flow apparatus and the response characteristics of commercial equipment are currently under investigation.

Analysis of NIH Program Activities

Project Description Sheet (continued)

SERIAL NO. NHI-34

Objectives: (continued)

4. In cooperation with Dr. Glenn Morrow, two different electronic switches were built to provide double channel monitoring with a single beam oscilloscope. One switch is of the alternate sweep type, the other a rapid switching "simultaneous" type. A paper on this device is being prepared for publication.

5. In cooperation with Dr. Stanley Sarnoff, a power supply and recording system was devised to enable polarographic recordings of blood oxygen to be made.

6. In cooperation with Dr. James O. Davis, a Sanborn Polyviso Recorder was modified to allow double beam monitoring on a single beam oscilloscope, to provide a specific pressure standardization on two channels, and to provide an accurate pressure averaging circuit.

Methods Employed: Cooperative projects with investigators in this and other laboratories are engaged upon utilizing the unique facilities of this laboratory.

Major Findings: The nature of this type of project is such that major findings are not to be expected.

Significance to HEART Research: The apparatus facilitates the work of the cooperating investigator.

Proposed Course of Project: The above listed projects have been completed. Others similar to this will be engaged upon during the coming year. A paper is being prepared on Item 4.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-34
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,600	2	2	4	0	.67	.67	
FY 1956	7,600	3	2	5	0	.67	.67	

12. _____
BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

R.P.C.-3

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-34
SERIAL NO.

16. None

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-35
SERIAL NO.

6. Development of Methods for Measurement of Blood Flow
PROJECT TITLE

7. Robert L. Bowman and Frank W. Noble
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate and develop practical methods for blood flow determination for application to physiological investigations.

Methods Employed: Two techniques for blood flow measurement that appear to be worth developing are (1) a velocity meter that measures the time for a warmed spot in the stream to pass a measured distance and (2) a meter that indicates mass flow by the force necessary to change angular momentum in an oscillating tube. The apparatus has been constructed and is ready for testing and development.

Major Findings: Both of these methods have been shown to operate well enough to deserve further development.

Significance to HEART Research: Dependable methods of metering blood flow are required in both the study of hemodynamics and in the metering of blood supplied to organs or individuals during study or surgical treatment.

Proposed course of project: To determine if these methods can be developed into dependable instruments for blood flow measurement and to develop the instrumentation, if indicated.

Budget Data Sheet

10. NHI-35
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$11,000	2	3	5	.33	1.34	1.67	
FY 1956	13,000	3	3	6	.33	1.34	1.67	

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI-35
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-36
SERIAL NO.

6. Development of Ultraviolet Photofluorimetry to Include Measurement of Ultraviolet Emission
PROJECT TITLE

7. Robert L. Bowman
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the extent to which substances that have absorption bands in the aid to far ultraviolet exhibit fluorescence in the ultraviolet region. Theoretical considerations suggest that a considerable number of these compounds are fluorescent or could be made to exhibit fluorescence spectra which would be of use in characterization and quantitation.

Methods Employed: The photofluorimeter has been left unchanged in its experimental arrangement to allow a number of projects of the Laboratory of Chemical Pharmacology to continue. The utility of the type of instrument proposed has been demonstrated and a paper on the Spectrophotofluorimetric Assay Throughout the Ultraviolet and Visible Range, by Bowman, Caulifield and Udenfriend has been submitted for publication. As the purpose of the research was to determine the utility of this type of instrumentation and as instruments based on this work are under commercial development by a number of companies, including Aminco and Farrand Optical Co., it is not considered worth while to build the final model in this laboratory.

Major Findings: The utility of both the method of determining the presence of invisible fluorescence in the ultraviolet and the scanning of fluorescent spectra has been established and the design requirements of a practical instrument worked out.

R.P.C.-1
December 1954

Project Description Sheet (continued)

NHI-36
SERIAL NO.

Significance to HEART Research: Spectrophotofluorimetric determination of qualitative characteristics of metabolites and chemical agents of interest to heart research facilitates the study of their disposition in the body. The method also facilitates the quantitative determination of these materials in body fluids.

Proposed course of project: This project is essentially complete but as new ideas and the need for adaptations for special problems arise, I expect to participate in further developments.

December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-36
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$2,800	1	0	1	.33	0	.33	
FY 1956	2,800	1	0	1	.33	0	.33	

12. _____
BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

R.P.C.-3
December 1954

Analysis of NIH Program Activities

Honors, Awards and Publications Sheet

15. NHI-36
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING
CALENDAR YEAR 1954:

"A paper entitled: Spectrophotofluorimetric Assay Throughout
the Ultraviolet and Visible Range. By
Bowman, Caulfield and Udenfriend, has been
submitted to Science for publication.

17. None

R.P.C.=1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-37
SERIAL NO.

6. Development of an Ultramicroanalytic Method for Sodium and Potassium Determination in Micropuncture Samples
PROJECT TITLE

7. Robert L. Bowman
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop an accurate dependable method of analysis of samples of 0.0001 and .01 μ L containing 50×10^{-12} to 150×10^{-10} moles of Na and 50×10^{-10} to 5×10^{-10} moles of K.

Methods Employed: The apparatus consisting of a microwave excitor cavity and the optical equipment necessary to produce intensity spectra for visual or photographic presentation is being used to (1) test the level of background emission of quartz tubes cleaned by various methods as compared to tubes similarly cleaned and dosed with a measured quantity of Na, K and Li (2) Determine the effect of residual gas on the emission spectra (3) Determination of the relative sensitivities of the Na, K and Li lines and the presence of interaction.

Major Findings: It appears that simple washings and high temperature baking in vacuum reduces the Na line to a level that can clearly be distinguished from a Na dose of 10^{-12} moles when similar excitation is used. The potassium sensitivity has not been clearly defined due to difficulties of line identification due to the fact that it is an invisible line and the absence of a suitable reference line for calibration. This difficulty will be resolved with spectrographs to be taken with the newly acquired Hilger spectrograph.

Analysis of NIH Program Activities

R.P.C.1

December 1954

Project Description Sheet (continued)

Major Findings: (continued)

Residual gas problems were encountered when the residual was mainly air as a number of air lines became prominent on excitation under certain conditions. The addition of argon in trace pressures has eliminated the problem and enhanced the sensitivity of the alkali lines in question.

The ultimate sensitivity of the lines does not appear to be measurable as the limit so far has been set by the presence of the lines in the blank tubes. This is true if high temperature excitation is utilized and as the lines appear to develop with time and temperature the background may be produced by the diffusion of Na and K from the body of the quartz into the cavity.

Significance to HEART Research: This method is to be applied to the micropuncture investigation of the handling of these cations by the kidney and its relation to water and electrolyte balances.

Proposed course of project: The development of the methods for the metals in question will be continued. An exploration of the potentialities of the method in regard to other metals and anions will be made as the work progresses. Methods utilizing the electrodeless discharge have been published for the halides which suggest that they may also be determined in the same way. Ca and Mg are also to be explored.

A few apparatus improvements are also required and are under construction, they are (a) replacement of the uniform field image converter with an electrostatic focused converter to reduce background noise now encountered due to field emission in the converter. (b) Replacement of the small grating with a high quality grating to obtain better line separation and higher sensitivity which will also improve the signal to noise ratio. (c) Reconstruction of vacuum system to obtain faster pumping and elimination of leaks.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-37
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,500	1	1	2	.33	.34	.67	
FY 1956	12,500	2	2	4	.83	.67	1.50	

12. _____
BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI-37
SERIAL NO.

16. None

17. None

December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE2. Laboratory of Technical Development
LABORATORY OR BRANCH5. NHI-38
SERIAL NO.6. Development of Methods for Determining Freezing Point Depression
PROJECT TITLE7. Robert L. Bowman
PRINCIPAL INVESTIGATOR(S)8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The method developed previously has been applied in a number of laboratories and is currently gaining acceptance, and the apparatus is currently available as a standard item from American Instrument Company. A need for micro methods in our own institute has prompted the design of a micro apparatus to be used in conjunction with the electronic bridge.

Methods Employed: A direct visualization of the final crystal of ice in a melting specimen was used in a method published by Ramsey in England, but the time per determination was excessive. The current approach is to use the same end point technique but replace his slow responding thermometer and water bath with a fast thermister system and provide a conducting metal block instead of a water bath.

Major Findings: The proposed system has been designed and is under construction.

Significance to HEART Research: Freezing point methods are of importance to determine the total osmotic activity in body fluids such as blood, urines, spinal fluid, etc.

Proposed course of project: To construct an apparatus as indicated and set up and test a suitable method for utilizing the instrument.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-38
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$4,600	1	1	2	.34	.33	.67	
FY 1956	10,600	2	1	3	1.34	.33	1.67	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION

REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. Unknown

R.P.C.-3

Analysis of NIH Program Activities

Honors, Awards and Publications Sheet

15. NO. NHI-38

16.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"An Instrument and Method for Rapid, Dependable Determination of Freezing Point Depression". The Journal of Laboratory and Clinical Medicine, Vol. 43, No. 2, Pages 310-315, Feb. 1954.

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-39
SERIAL NO.

6. Analysis of Deuterium Concentration in Blood and Aqueous Solutions
PROJECT TITLE

7. Harold J. Morowitz
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

Objectives: To apply the optical spectroscopic and other methods of deuterium analysis to measurement of water content, water transport and the physical state of water in biological systems.

Methods Employed: 1. Optical spectroscopic deuterium analysis.
2. Falling drop method of deuterium oxide analysis.

Major Findings: 1. Determination of water content of red blood cells.
2. Hydrogen exchange of hemoglobin and related molecules.

Significance to HEART Research: The problem of measuring water content of tissues is a general one in both clinical and research medicine. Any improvement of existing techniques is welcomed by investigators in these fields.

Proposed course of project: Principal investigator is leaving January 21, 1955. The project is nearly complete and material is being prepared for publication.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-39
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT TOTAL DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$2,800	1	0	1	.33	0	.33	
FY 1956	0	0	0	0	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. Unknown

R.P.C.-3

December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NHI-39
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Hydrogen exchange of Amino Acids, Peptides, Proteins and Related Molecules" (accepted for publication by Archives of Biochemistry and Biophysics)

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH
5. NHI-40
SERIAL NO.

6. Hydration of Proteins and Other Biological Molecules. Interaction of Proteins with Smaller Molecules
PROJECT TITLE

7. Harold J. Morowitz
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the thermodynamics and molecular interactions between large biological molecules such as proteins and nucleic acids and smaller molecules such as water urea salts, etc.

Methods Employed: 1. Adsorption - desorption isotherms.

- a. Equilibrium vapor pressure
- b. Equilibrium dialysis

2. Water replacement in growing cells.

Major Findings: A. Detailed adsorption desorption isotherms have been obtained for water binding to the following systems.

- 1. Bovine serum albumin
- 2. Bovine serum albumin and urea
- 3. Human red blood cells (normal and sickled)
- 4. Highly polymerized desoxiribonucleic acid
- 5. Sodium ribonucleate

B. Isotherms at three temperatures have been obtained for the system Methyl Orange-Bovine Plasma Albumin using the equilibrium dialysis method.

C. Water replacement techniques in growing cells have been investigated using glycerine and *B. subtilis* and *E. coli*. It has been possible to adapt cells to concentrations of 30% glycerine and it has been demonstrated that the intracellular and extracellular concentrations are approximately the same.

Significance to HEART Research: This project should provide certain basic findings which apply to the study of water metabolism of normal and pathological cells and tissues. Such factors are related to kidney function, edema, etc.

Proposed course of project: Principal investigator is leaving as of January 21, 1955.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-40
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$6,000	1	1	2	.34	.33	.67	
FY 1956	0	0	0	0	0	0	0	

12. _____
BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. Unknown

R.P.C.-3
December 1954

7
Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-40
SERIAL NO.

16. None

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-41
SERIAL NO.

6. Instrumentation for Membrometry, the Study of Solvent Transport through
Membranes under Hydrostatic Pressure
PROJECT TITLE

NHI-11

7. Harold J. Morowitz (Technical Development) Adrian Hogben (K. & E. Lab.)
PRINCIPAL INVESTIGATOR(S)

8. OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To design and construct an instrument for the simultaneous measurement of pressure and flow across a membrane.

Method Employed: Design of instrument including, strain gage, microburette, constant speed motor, etc.

Major Findings: The instrument has been designed, built and tested. It is now being applied to problems of membrane physiology.

Significance to HEART Research: This is applicable to problems of water transport encountered in the kidneys, blood vessels and other organs.

Proposed course of project: Project will be continued under direction of Dr. Adrian Hogben of K & E Laboratory

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-41
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$1,000	1	0	1	0	0	0	
FY 1956	0	0	0	0	0	0	0	

12. _____
BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-41
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH
5. NHI-42
SERIAL NO.
6. Physics of Ultra-rapid Freezing of Water, Colloidal Solutions and Protoplasm
PROJECT TITLE
7. John L. Stephenson
PRINCIPAL INVESTIGATOR(S)
8. _____
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: (1) To investigate the basic physics of the rapid freezing process in water, colloidal solutions and protoplasm. (2) To apply this information to the analysis of hydration phenomena in protoplasm. (3) To extend the range of application of freezing and drying as a method of fixation and preservation of biological material.

Methods Employed: Experimental methods for measuring the heat production during cooling have been worked out. As a preliminary part of the problem the cooling properties of various materials--namely, isopentane and liquid propane cooled in liquid nitrogen, and liquid nitrogen have been studied. The theory of the cooling process itself has been examined and an approximate relation between the heat constants of the system being cooled, the heat constants of the coolant and the velocity of stirring has been obtained. There seems to be a reasonable, although possibly heuristic, agreement between theory and experiment.

Major Findings: The theory of the rapid freezing has been extended to relate the final size and number of ice crystals and the best production during freezing to the absolute rate of nucleation as a function of temperature and the rate of radial growth of these nuclei. By determining these factors, of basic physics-chemical interest in themselves, it should be possible to predict

Major Findings (continued)

the freezing velocity necessary to achieve "vitrification" of water and other materials. It should also be possible to determine to what extent actual material rapidly cooled to very low temperatures falls short of this ideal.

The cooling properties of isopentane, liquid propane and liquid nitrogen have been measured. Liquid propane has been found to be the best coolant.

Significance to HEART Research: (1) To investigate the basic physics of the rapid freezing process in water, colloidal solutions and protoplasm. (2) To apply this information to the analysis of hydration phenomena in protoplasm. (3) To extend the range of application of freezing and drying as a method of fixation and preservation of biological material.

Proposed course of projects: Cooling curves of water and tissues are being obtained. The final size and number of ice crystals of tissue with known cooling curves will be measured. These data will be analyzed using the above-mentioned theory.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-42
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,000	1	1	2	.34	.33	.67	
FY 1956	10,000	2	2	4	1.00	.67	1.67	

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI-42
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Caution in the Use of Liquid Propane for Freezing Biological Specimens - Nature 174:235 (1954)

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-43
SERIAL NO.

6. Ultraviolet Microspectrometry
TITLE OF PROJECT

7. John L. Stephenson
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop techniques of ultraviolet microspectrometry for intracellular studies.

Methods Employed: Ultraviolet light from a monochromator is passed through a microscopic system and onto a detector (usually a photomultiplier). Thus permitting extensive coefficients of very small samples to be determined.

Major Findings: None

Significance to HEART Research: Would facilitate study of intracellular nucleoproteins.

Proposed course of project: Temporarily discontinued because of lack of personnel.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-43
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	0	0	0	0	0	0	0	
FY 1956	\$7,400	2	2	4	.67	.67	1.34	

12. _____
BUDGET ACTIVITY

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-43
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-44
SERIAL NO.

6. Electron Microscopy
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further the application of electron microscopy to cytological problems.

Methods Employed: Thin sections of biological material fixed by freezing, then dried, are examined in the electron microscope. Various staining procedures to heighten contrast have been tried.

Major Findings: In collaboration with Dr. Isidore Gersh at the University of Chicago techniques for the electron microscopy of frozen-dried material are being worked out. The work at this laboratory is centered on the physics of the rapid freezing process; the electron microscopy is being done at the University of Chicago.

Significance to HEART Research: Suitable procedures in electron microscopic study of tissues will make possible a submicroscopic pathology of cardiovascular disease.

Proposed course of project: Continued work in same general direction in cooperation with Dr. Gersh's laboratory.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-44
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		PATIENT TOTAL DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	
FY 1955	\$2,900	1	0	1	.33	0	.33
FY 1956	2,900	1	0	1	.33	0	.33

12. _____
BUDGET ACTIVITY

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. _____
IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

This is a cooperative study with Dr. Isidore Gersh, Department of Anatomy, University of Chicago.

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-44
SERIAL NO.

16. None

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-45
SERIAL NO.

6. Infra-Red Microspectrometer
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop an infra-red spectrometer suitable for obtaining absorption spectra of tissues and cells.

Methods Employed: Infra-red radiation from a monochromator is passed through a reflecting microscope and into a suitable detector. Thus permitting absorption spectra of microscopic samples to be obtained.

Major Findings: None

Significance to HEART Research: If techniques can be developed, may be useful in study of intracellular metabolism.

Proposed course of project: Instrument is being completed.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-45
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$2,800	1	0	1	.33	0	.33	
FY 1956	2,800	1	0	1	.33	0	.33	

12. _____
BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. Unknown

R.P.C.=3

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI-45
SERIAL NO.

16. None

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-46
SERIAL NO.

6. Drying of Tissues
PROJECT TITLE

7. John L. Stephenson
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To obtain information on the nature of the solid liquid interface in protoplasm.

Methods Employed: A drying apparatus has been set up in which small samples of tissue can be dried at temperatures varying from above room temperature to the temperature of liquid nitrogen, while recording their weight and temperature.

Systems for the automatic recording of the weight and temperature have been developed. The temperature recording system utilizes more or less standard techniques. The e.m.f. difference between a thermocouple embedded in the tissue and a reference couple is fed into a galvanometer is replaced with a Leeds and Northrup d. c. amplifier. The output from this goes into a chart recorder. Full range in the recorder can be varied from 1 to 25 degrees centigrade. The system is relatively free from drift which is of the order of 1 or 2% over a 24 hour period.

The weight recording systems utilizes an old Cambridge 12 cm. strip camera. The image from the cross hair on a delicate spring balance inside the vacuum chamber is projected on the moving film after being rotated 90° in order to convert vertical into horizontal motion. The zero of the system is adjusted by moving the telescope which is mounted on a micrometer slide. This also gives periodic absolute measurements of position. At present

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet-(continued)

NHI-46

the system operates at an optical magnification of about 100. The resolution of the photographic recording is about 1 mm. Using a spring with an elongation of 5 cms. per gram, a weight change of 1/5000 gram can be detected. It is possible that with sufficient isolation of the system from vibration the resolution can be increased by another factor of five.

Major Findings: None

Significance to HEART Research: By increasing information on basic organisation protoplasm.

Proposed course of project: Delicate quartz springs have been obtained and a system has been designed which permits isolation from vibration. It is hoped with the improved system to measure weight changes of the order of 0.1 to .01 micrograms, which will make possible obtaining drying curves on extremely minute samples by direct measurement.

On such small samples simultaneous recording of temperature is not possible, but the drying information can be correlated with the information obtained from temperature measurements of nearly identical samples.

It is also planned to correlate these studies with vapor pressure measurements during drying. Equipment for this has been assembled and is ready to set up.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-46
SERIAL NO.

11. BUDGET DATA:

FY	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$2,800	1	1	2	0	.33	.33	
FY 1956	4,800	1	1	2	0	.33	.33	

12. RESEARCH ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) ITEM

Dr. Isidore Gersh, Department of Anatomy, University of Chicago.

14. NONE

R.P.C.-3
December 1954

Analysis of NIH Program Activities

Honors, Awards and Publications Sheet

15. NHI-46
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Theory of the Vacuum Drying of Frozen Tissues" John L. Stephenson
Bull. Math. Biophys. 15:411-429 (1953)

"Theory for the Design of Apparatus for Drying Frozen Tissues"
John L. Stephenson Bull. Math. Biophys. 16:23-43 (1954)

"Freezing and Drying of Tissues for Morphological and Histochemical Studies" Isidore Gersh and John L. Stephenson in BIOLOGICAL APPLICATIONS OF FREEZING AND DRYING. Edited by R. J. C. Harris. Academic Press (1954) p. 329-384.

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Technical Development
LABORATORY OR BRANCH

5. NHI-47
SERIAL NO.

6. Development of a Self-Balancing Potentiometer
PROJECT TITLE

7. John L. Stephenson, Frank W. Noble, Robert L. Bowman
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop a potentiometer type circuit of high sensitivity and rapid response, for the measurement of rapid cooling curves, occurring in one second or less and having rapid transients in various parts of the curve.

Methods Employed: One scheme which has been tried and appears to have considerable promise is using a string galvanometer with a photoelectric following system. The applied signal causes the shadow of the string to move across two balanced photomultiplier tubes. This generates a signal, a fraction of which, (1/100,000 to 1/1,000) is used to counteract the motion of the string. Balance is achieved when no current is flowing through the string or when the counter signal exactly equals the applied. The entire signal is then further amplified by a cathode ray oscilloscope.

Major Findings: Preliminary tests indicate the system has a balancing time of about 1/100 of a second, a noise level of about 5 microvolts and drift of less than 10 microvolts per hour. It is presently limited by a tendency to oscillate at about 300 cycle.

Significance to HEART Research: If such an instrument can be perfected, it should be ideal for measuring any bioelectric phenomenon in which both initial transient and d.c. after potential are of interest.

Proposed course of project: A preliminary model has been developed and will be explored and tested. By providing suitable oil or E. M. damping an attempt will be made to increase frequency response.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-47
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$9,200	3	4	7	0	1.33	1.33	
FY 1956	9,200	3	4	7	0	1.33	1.33	

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. Unknown

R.P.C.-3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NMI-47
SERIAL No.

16. None

17. None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Clinical Endocrinology
Section
5. NHI-48C
Serial No.
6. Study of Sodium Retaining Activity in Patients Who Form Edema
Project Title
7. Leroy E. Duncan, Jr., M. D.
Principal Investigator
8. Grant W. Liddle, M. D.
Other Investigator

9. PROJECT DESCRIPTION:

Project: Study of Urinary Sodium Retaining Activity in Patients Who Form Edema.

Objectives: To clarify the role of the adrenal gland in the formation of edema.

Methods Employed: Various types of extraction procedures have been studied. Urine has been circulated through methylene chloride; methylene chloride has been circulated through urine by distillation and condensation in a Hirsdirbers-Wolfe apparatus, and urine and methylene chloride have been circulated through the extraction column of a counter current extraction apparatus. The last type of extraction is unsatisfactory since it is little if any more efficient in the extraction of sodium retaining activity, but a great deal more efficient in the extraction of contaminating materials. The most satisfactory method of extraction is the circulation of urine through methylene chloride with a pump. It was found that there was considerable loss of sodium retaining activity in urinary extracts subjected to paper chromatography. The method at present in use for determination of sodium retaining activity is: (1) acidification of the urine to pH 1; (2) extraction by circulating urine through methylene chloride for 22 hours; (3) washing with dilute alkali and water; (4) evaporation to dryness and solution in ethanol, and (5) bioassay.

Patient Material (calendar year 1954):

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult Males	3	30
Adult Females	0	
Outpatient: Number of Patients	0	

R.P.C.-1
December 1954
NHI-48C (Continued)

Major Findings: With this method the correlation between the amount of edema, the urinary output of sodium and the uptake of sodium by ingested cation-exchange resin is being studied. The first patient studied had hepatic cirrhosis. In the first period while edema-free and with only slight ascites, he had a low urinary sodium, a low uptake of sodium by resin and high urinary sodium retaining activity. The patient was then given edema and gross ascites by intravenous infusion of saline. He was studied while in this condition and was found to have a higher urinary output of sodium, a higher uptake of sodium by resin, and a lower urinary output of sodium-retaining activity. The ascites was removed by paracentesis and the patient was studied in a third period. The findings were the same as in the first cellular fluid volume in the edematous patient in some way reduces the amount of circulating retaining material (presumably aldosterone) and thus leads to an increased uptake of sodium by resin in the intestine and in increased urinary excretion of sodium.

Significance to Heart Research: This work may lead to an increased understanding of the mechanisms of heart failure.

Proposed Course of Project: Repetition of the experiment just described in normals and in patients with cirrhosis and congestive cardiac failure is planned. Study of the effect of digitalization on the urinary output of sodium retaining activity is also being set into operation.

R.P.C.=2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-48C
Serial No.

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 13,700	2	2	4	.83	1.00	1.83	700
FY 1956	\$ 13,700	2	2	4	.83	1.00	1.83	800

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-48C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Experimental Therapeutics Section
5. NHI-49C
Serial No.
6. Obesity and Heart Disease
Project Title
7. Albert Sjoerdsma, M. D. and Luther L. Terry, M. D.
Principal Investigator(s)
8. None
Other Investigator(s)

9. PROJECT DESCRIPTION:

Project: Obesity and Heart Disease.

Objectives: To attempt to discover the possible relationships between obesity and heart disease.

Methods Employed: Studies of water diuresis were performed on patients with obesity, on controls and on one patient with diabetes insipidus.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	1	30
Adult females	9	
Outpatient: Number of patients	39	
Number of visits	45	

Major Findings: It has been found that standing is associated with antidiuresis in obesity. The rise in urine osmolarity accompanying the fall in urine volume suggests antidiuretic hormone (ADH) activity is responsible. The controls studied showed no increase in urine osmolarity associated with the decrease of urine flow during one hour of motionless standing, suggesting that the antidiuresis in this instance is due to other causes than ADH activity. To demonstrate the antidiuresis occurring on standing in the absence of ADH, the patient with diabetes insipidus was studied and demonstrated again the antidiuresis of the upright position.

Significance to Heart Research: Clinicians have maintained for a long period of time that obesity definitely increases the severity of patients with heart disease. There are further suggestions that obesity may, in some fashion, be a primary factor in the production of heart disease. This subject has not been thoroughly investigated with modern physiological methods. It is, therefore, of great importance to obtain as

R.P.C. - 1

NHI-49C

Significance to Heart Research (Continued):

much direct information on this subject as can be obtained with present methods of investigation.

Proposed Course of Project: It is felt that there is much need for further exploration of the subject, particularly with regards to the hemodynamic and pulmonary features of obesity.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-49C
Serial No.

11. Budget Data:

	: Estimated : Expenditures	: Positions			: Man Years			: Patient : Days
		: Prof	: Other	: Total	: Prof	: Other	: Total	
FY 1955	: \$11,700	: 2	: 1	: 3	: .83	: 1.00	: 1.83	: 1,000
FY 1956	: \$14,200	: 3	: 1	: 4	: 1.83	: 1.00	: 2.83	: 1,100

12. Budget Activity:

Research Administration
Review & Approval Technical Assistance

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-49C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Clinical Endocrinology
Section
5. NHI-50C
Serial No.
6. Studies on the Pathogenesis of Diabetes Insipidus and of Renal Tubular
Solute and Water Reabsorption in the Absence of Antidiuretic Hormone.
Title of Project
7. Frederic C. Bartter, M. D.
Principal Investigator
8. Catherine S. Delea, B. S.
Other Investigator

9. PROJECT DESCRIPTION:

Project: Studies on the pathogenesis of diabetes insipidus and of renal tubular solute and water reabsorption in the absence of antidiuretic hormone.

Objectives: 1. To elucidate the pathogenesis of diabetes insipidus in man.

2. To examine the role of "distal tubular solute reabsorption" in the clearance of "free water" in the absence of antidiuretic hormone.

Methods Employed: To date two patients with diabetes insipidus have been studied. One was an adult and the other, a child with pitressin-resistant diabetes. Further clinical studies are planned to repeat and extend this investigation.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions: Adult Males	0	
Adult Females	1	60
Children Male	0	
Children Female	1	60
Outpatient: Number of Patients	3	
Number of visits	8	

Major Findings: The adult patient with diabetes insipidus was shown to be unable to produce concentrated urine upon dehydration or upon infusion of hypertonic saline, both of which procedures raised serum osmolarity by 30 milliosmoles. On quiet standing, however, she did produce markedly hypertonic urine together with a 50-per-cent fall in glomerular filtration rate. In the child with pitressin-resistant diabetes insipidus, quiet standing produced no fall in glomerular

R.P.C. - 1
December 1954
NHI-50C

Major Findings (Continued):

diabetes insipidus, quiet standing produced no fall in glomerular filtration rate and no urine hyperosmolarity. (In studies done by Dr. Hans G. Keitel, NHI, dehydration had failed to produce hypertonicity of the urine in this patient as had pitressin administration).

It is not clear whether the former patient could produce ADH under the stimulus of quiet standing, or could produce concentrated urine in its absence. In future studies, nicotine and acetyl choline will be used in an attempt to answer this question. Filtration rates will also be determined during dehydration.

In studies done with Dr. Jack Orloff, NHI, the effect of osmotic diuresis produced by mannitol was observed in these patients on low and high salt sodium intakes. It was thought that on the low intake, the distal tubules might be reabsorbing sodium at submaximal rates and still be capable of absorbing additional sodium made available by mannitol diuresis. This would increase "free water" clearance correspondingly. The results were equivocal: in the adult patient, free water clearance was increased by the mannitol on the low, but not on the high, sodium diet; in the child, there was some rise on both diets without clear-cut differences.

Significance to Heart Research: These studies are a part of the general program designed to elucidate the mechanisms of the abnormal salt and water metabolism in edematous states.

Proposed Course of Project: It is planned to repeat and to extend these studies. The question of the intrinsic ability of the kidney to produce a concentrated urine in the absence of the antidiuretic hormone is presently being examined in dogs with diabetes insipidus.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-50C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 10,000	2	1	3	.67	.50	1.17	750
FY 1956	\$ 13,000	2	2	4	.67	.83	1.50	750

12. Budget Activity:

Research	<input checked="" type="checkbox"/>	Administration	<input type="checkbox"/>
Review & Approval	<input type="checkbox"/>	Technical Assistance	<input type="checkbox"/>

13. Identify any cooperating units of the Public Health Service, or other organizations, providing funds, facilities, or personnel for this project in either 1955 or 1956:

Refer to NHI-1C (Kidney and Electrolyte Metabolism - Doctors Orloff, Keitel and Walzer).

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-50C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Clinical Endocrinology Section
5. NHI-51C Serial No.
6. The Role of Adrenal Cortical Steroids in Salt Retention of Edematous States
Project Title
7. Grant W. Liddle, M. D.
Principal Investigator
8. None
Other Investigator(s)

9. PROJECT DESCRIPTION:

Project: The Role of the Adrenal Cortical Steroids in the Salt Retention of the Edematous States.

Objectives: To improve wherever possible the assay method for aldosterone and similar steroids and to study the mechanism regulating aldosterone production by the adrenal gland in health and disease.

Methods Employed: A colony of adrenalectomized dogs has been established and the productivity of the assay laboratory has reached a satisfactory level. Crystalline aldosterone has been procured and the pattern of the response to aldosterone in doses ranging from 1 to 30 micrograms has been studied systematically in order to select the most sensitive and reliable parameters for bioassay purposes. A thorough study demonstrating the similarity of the effects on electrolyte excretion exerted by appropriate doses of aldosterone, desoxycorticosterone and an extract of urine from edematous patients. Also two normal volunteers and one patient with cirrhosis have been studied.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult Males	8	60
Adult Females	1	60
Outpatient: Number of Patients	3	
Number of Visits	4	

Major Findings: In studies on patients the following results were obtained:

<u>Treatment</u>	<u>Effect on "Aldosterone" Excretion</u>	<u>Effect on "Hydrocortisone" Production</u>
Na ⁺ deprivation	Increased	No effect
Na ⁺ loading	Decreased	No effect
Exogenous ACTH	No effect	Increased
Suppression of exogenous ACTH	No effect	Decreased

The conclusion seems to be established that aldosterone production and hydrocortisone production by the adrenal gland are regulated by separate mechanisms.

Significance to Heart Research: It is anticipated that this study will give us a better understanding of the mechanisms of salt and water retention in congestive heart failure.

Proposed Course of Project: To investigate the behavior of steroid mixtures in the above assay animals. To gain a more specific insight into the mechanisms regulating aldosterone production. To offer continuing assistance to Doctors Duncan, Bartter and Pechet in studies related to salt excretion.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-51C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$19,100	1	2	3	.50	2.50	3.00	750
FY 1956	\$19,100	1	2	3	.50	2.50	3.00	750

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-510
Serial No.

16. List Publications Other than Abstracts from this Project during Calendar Year 1954:

Liddle, R. W.; Pechet, M. M., and Bartter, F. C.: Enhancement of Biological Activities of Corticosteroids by Substitution of Halogen Atoms in 9-Alpha Position, Science, 120:496 (September 24) 1954.

17. None.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Clinical Endocrinology
Section
5. NHI-52C
Serial No.
6. A Study of the Edematous Patient and A Clinical Study of Steroids and Steroid
Metabolism.
Project Title
7. Maurice M. Pechet, M. D.
Principal Investigator
8. None
Other Investigators
9. PROJECT DESCRIPTION:

Project: This study is twofold; a study of the edematous patient, and a clinical study of steroids and steroid metabolism.

Objectives: Investigation of methods for the isolation of aldosterone from biologic fluids. To study methods for measuring the level of aldosterone in biologic fluids and to investigate the parameters influencing the secretion of aldosterone in normals and in diseased individuals.

To study clinically the metabolism of two new steroids: metacortandracin and metacortandralone in various diseased states. To perform metabolic balance studies with these new steroids.

Methods Employed: For the isolation and characterization of aldosterone by paper chromatography 70 solvent systems were investigated thoroughly and new solvent systems were evolved for the separation of polar steroids. A new assay method for aldosterone and other adrenal cortical steroids was investigated in collaboration with Doctor Hajdu. Further studies were undertaken in two cirrhotic patients to study the influence of ACTH, cortisone, hydrocortisone, metacortandracin and metacortandralone on the level of secretion of aldosterone.

Complete metabolic balance studies were carried out on two arthritic patients on Doctor Bunim's service with metacortandracin and metacortandralone. Electrolyte balance studies were performed on two other arthritic patients. Studies on the metabolism of metacortandracin and metacortandralone were undertaken in various disease states. Complete metabolic studies are in progress in a normal and in an Addisonian patient.

R.P.C. = 1
December 1954
NHI-52C (Continued)

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	2	30
Adult females	4	30
Outpatient: number of patients	10	
number of visits	21	

Major Findings:

1. The mobility of the active urinary salt-retaining factor is identical with that of aldosterone.
2. Preliminary results during administration of ACTH, hydrocortisone and salt point to a decreased urinary level of aldosterone.
3. In studies on the Addisonian patient the following effects were noted:
 - A. Suppression of the adrenals as evidenced by decrease in urinary 17-ketosteroids.
 - B. In a normal at 70-milligram-dose a diuresis of nitrogen occurs. At 30-milligram-dose the nitrogen loss is much less.
 - C. In a normal, after a delay period of two to three days, there is a diuresis of sodium which is of considerable magnitude at the 70-milligram dose.
 - D. The urinary nitrogen loss is more readily discernible in a normal individual than in an arthritic patient.

Significance to Heart Research: It is anticipated that this study will further elucidate factors pertaining to the edematous state in heart disease.

Proposed Course of Project: It is planned to continue and to extend the above studies when further patients become available for research.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-52C
Serial No.

11. Budget Data:

	Estimated Expenditures	Positions			Man Years			Patients Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$ 12,700	1	1	2	1.00	1.00	2.00	1,000
FY 1956	\$ 12,700	1	1	2	1.00	1.00	2.00	1,000

12. Budget Activity:

Research Administration
 Review & Approval Technical Assistance

13. Identify any cooperating units of the Public Health Service or other organizations providing funds, facilities, or personnel for this project in either 1955 or 1956: If cooperating unit is within NIH indicate serial No.

Refer to National Institute of Arthritis and Metabolic Diseases (#62131-94)
 Dr. Joseph J. Bunim.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI-52C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Clinical Endocrinology Section
5. NHI-53C
Serial No.
6. Adrenal Cortical Steroids
Project Title
7. Frederic C. Bartter, M. D.
Principal Investigator
8. Catherine S. Delea, B. S.
Other Investigator(s)
9. PROJECT DESCRIPTION:

Project: The evaluation of the effects of salt-retaining steroids in patients with Addison's disease and the investigation of the physiological stimuli to aldosterone secretion and salt retention.

Objectives: To evaluate and to study the effects of salt-retaining steroids in patients with Addison's disease. To investigate the physiological stimuli to aldosterone secretion and salt retention and to determine the effects of alterations of body fluid volume on aldosterone secretion.

Methods Employed: 1. Renal function studies were done in a patient with Addison's disease, and 9-alpha fluoro hydrocorticosterone and aldosterone were injected intravenously after control periods had been observed.

2. A patient was given pitressin tannate in oil while on a low sodium diet, on balance regimen, to determine whether a fall of urinary aldosterone could be shown to accompany the sodium loss so produced.

3. A patient was given a low potassium diet while on a low sodium diet to determine whether urinary aldosterone excretion could be depressed.

Patient Material (1954 calendar year):

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Male Patients	0	
Female Patients	2	60
Outpatient: Number of Patients	1	
Number of visits	32	

Major Findings: In No. 1 (under "Methods Employed") the first studies disclosed no clear-cut effects upon sodium or potassium or filtrable acidity: there was a fall of sodium excretion, but the patient showed a similar fall when no steroid was given. It was concluded that larger doses be given and the observations period extended considerably longer. In a latter study with aldosterone in an Addisonian patient made acidotic, sodium retention and fall of urine pH followed the administration of aldosterone.

Study No. 2 had to be terminated due to the development of complications. A fall of aldosterone was determined, albeit not a highly significant fall by statistical criteria.

A depression was observed in the patient in study No. 3 given a low potassium diet, the exact significance of which is being determined.

Significance to Heart Research: These studies are part of the general program designed to elucidate the mechanisms of edema formation in cardiac diseases.

Proposed Course of Project: The pitressin studies will be extended. The effects of high and low sodium intake combined with low and high potassium intake will be compared. Attempts will be made to determine the effects of alterations of body fluid volume on aldosterone secretion.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-53C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$16,500	2	4	6	.33	2.17	3.00	365
FY 1956	\$16,500	2	4	6	.33	2.17	3.00	500

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-53C
Serial No.

16. List Publications Other than Abstracts from this Project During Calendar Year 1954:

Liddle, G. W.; Pechet, M. M., and Bartter, F. C.: Enhancement of Biological Activities of Corticosteroids by Substitution of Halogen Atoms in 9-Alpha Position, Science, 120:496 (September 24) 1954.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Clinical Endocrinology
Section
5. NHI-54C
Serial No.
6. Study of the Effect of Pyrogenic Reactions and Sterile Inflammatory Processes on Hypertension.
Project Title
7. Leroy E. Duncan, Jr., M. D.
Principal Investigator
8. None
Other Investigator(s)
9. PROJECT DESCRIPTION:

Project: The study of the effect of pyrogenic reactions and sterile inflammatory processes on hypertension.

Objectives: The intravenous injection of certain materials extracted from bacteria is followed by fever and a reduction of the blood pressure of hypertensive patients or animals to or towards normal. If fever is prevented by the administration of acetyl salicylic acid, the reduction in blood pressure still occurs. Also the production of sterile abscesses in dogs with renal hypertension is followed by reduction of blood pressure to or toward normal. The present project is undertaken in order to learn something about the mechanical involvement in this process.

Methods Employed: One patient was injected repeatedly with Piromen (a pyrogenic extract of Pseudomonas) incubated with her serum. This was done to test the statement in the literature that tolerance which develops to the injection of bacterial pyrogens can be greatly reduced or abolished in rabbits by the incubation of the pyrogen with the rabbit's serum prior to injection.

Patient Material: (calendar year 1954)

	<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions: Adult Males	0	
Adult Females	1	60
Outpatient: Number of patients	0	

R.P.C. - 1
December 1954
NHI-54C (Continued)

Major Findings: It was found that following injection, this patient rapidly developed tolerance to the injected material.

Significance to Heart Research: This work may increase our understanding of the mechanisms of this pyrogenic reaction which has been used in the treatment of hypertension.

Projected Course of Project: Dogs are being made hypertensive by unilateral nephrectomy and partial occlusion of the artery to the remaining kidney. Sterile abscesses will be induced in these dogs. When they become normotensive, they will be cross-circulated with other renal hypertensive dogs to determine whether a humoral agent is involved in the reduction of pressure.

R.P.C. 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-54C
Serial No.

11. Budget Data:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$ 10,200	1	2	3	.33	1.00	1.33	700
FY 1956	\$ 10,200	1	2	3	.33	1.00	1.33	800

12. Budget Activity:

Research	<input checked="" type="checkbox"/>	Administration	<input type="checkbox"/>
Review & Approval	<input type="checkbox"/>	Technical Assistance	<input type="checkbox"/>

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-54C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Clinical Endocrinology
Section
5. NHI-55C
Serial No.
6. Action of Parathyroid Hormone
Project Title
7. Frederic C. Bartter, M. D.
Principal Investigator
8. Catherine S. Delea, B. S.
Other Investigator

9. PROJECT DESCRIPTION:

Project: The Action of the Parathyroid Hormone.

Objectives: To study the physiology of the parathyroid gland and the mechanism of action of the parathyroid hormone.

Methods Employed: The effect of parathyroid extract is determined in patients with surgical hypoparathyroidism during renal clearance studies by a technique analagous to that reported with dog studies.

Patient Material (calendar year - 1954):

	<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions: Adult Males	0	
Adult Females	1	60
Outpatient: Number of patients	1	
Number of visits	20	

Major Findings: The effect was found to be the same as that previously reported in dogs: P excretion occurred without increase of filtration rate or filtered P load, resulting entirely from decrease of P reabsorption.

Significance to Heart Research: This study is one of basic physiology. It has direct bearing on the physiology of renal function and mechanisms concerned in phosphate metabolism.

Proposed Course of Project: It is planned to extend the above observations to determine the effect of chemical and physical alterations of parathyroid extract on its actions on kidneys and on bone.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-55C
 Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 19,200	2	4	6	.67	2.00	2.67	200
FY 1956	\$ 19,200	2	4	6	.67	2.00	2.67	250

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-55C
Serial No.

16. None.

17. List Honors and Awards to Personnel Relating to this Project During Calendar Year 1954:

Principal Investigator of this project is a member of
the Peripatetic Club.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Clinical Endocrinology Section
5. NHI-56C Serial No.
6. Studies on the Fate of Plasma Protein Administered Intravenously with Especial Reference to the Etiology of Clinical Hypoproteinemia.
Project Title
7. Frederic C. Bartter, M. D.
Principal Investigator
8. Catherine S. Delea, B. S.
Other Investigator

9. PROJECT DESCRIPTION:

Project: The study of the fate of plasma protein administered intravenously with especial reference to the etiology of clinical hypoproteinemia.

Objectives: To elucidate the pathogenesis of clinical hypoproteinemia by estimating the rate of destruction of human serum albumin administered intravenously to a hypoproteinemic subject on balance regimen. In a study on a previous patient the primary defect appeared to be an increased rate of destruction of plasma protein.

Methods Employed: A 29-year-old woman with severe hypoalbuminemia and edema with massive obesity of the legs and buttocks with normal distribution above these regions was studied. Liver function and renal function tests gave normal results. On balance regimen with constant daily food and water intake she was observed for 36 days as follows:

"Three 4-day control periods, three 4-day periods during which 50 grams of human salt-poor albumin was administered daily by vein, and 4-day periods on no treatment. Daily determinations of urinary N, Na, K, Cl, and P were done, and 2-day determinations of urinary Ca. N, Na, K, P, and Ca were also determined in sample diets and in 4-day stool periods."

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult Males	0	
Adult Females	1	45
Outpatient: Number of Patients	1	
Number of Visits	22	

R.P.C. - 1
December 1954
NHI-56C (Continued)

Major Findings: In the analysis of both studies it was found that this patient showed less "burning" of administered albumin than any patient previously studied with this technique. There was actually a fall of urine N during albumin administration. This patient showed more conversion of administered albumin than any patient previously studied by this technique.

In these studies, "burning" is measured by the increase in urinary N and "conversion" (i.e., to protoplasm) by retention of P, corrected for Ca. Thus, these results could represent conversion of the albumin to "protoplasm," or, alternatively, "burning" of the albumin accompanied by an equivalent decrease in catabolism of protoplasm -- anabolism remaining unchanged.

Since the dietary intake was constant throughout, and the caloric contribution from nitrogenous components actually fell with albumin, it is tempting to believe that fat catabolism was correspondingly increased. In the second study urinary ketone bodies were determined. They showed a slight fall during the administration of albumin. The rate of destruction of the administered albumin was measured directly and the findings confirm those derived from the two metabolic studies. It was found that the rate of destruction was approximately half the normal rate. This furnishes additional evidence that the defect in this patient is one of albumin formation rather than one of albumin destruction.

Significance to Heart Research: This is a study of protein metabolism in one edematous state. The results of the study have bearing on the interpretation of all states of edema which is an essential part of the heart program.

Proposed Course of Project: It is proposed to extend the above observations when other patients become available.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-56C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 17,000	3	3	6	1.17	1.16	2.33	300
FY 1956	\$ 17,000	3	3	6	1.17	1.16	2.33	500

12. Budget Activity:

Research	<input checked="" type="checkbox"/>	Administration	<input type="checkbox"/>
Review & Approval	<input type="checkbox"/>	Technical Assistance	<input type="checkbox"/>

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-56C
Serial No.

16. List publications other than abstracts from this project during calendar year 1954:

Albright, F.; Bartter, F. C.; Dempsey, E. F.; Forbes, A. P.; Henneman, P. H., and Reifstein, E. C., Jr: Serum Albumin and Bone Matrix, Trans. 5th Conf. on Metabolic Interrelations, Josiah Macy Foundation, p. 277, 1954.

17. None.

R.F.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-56C
Serial No.

16. List publications other than abstracts from this project during calendar year 1954:

Albright, F.; Bartter, F. C.; Dempsey, E. F.; Forbes, A. P.; Henneman, P. H., and Reifenshtein, E. C., Jr: Serum Albumin and Bone Matrix, Trans. 5th Conf. on Metabolic Interrelations, Josiah Macy Foundation, p. 277, 1954.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Clinical Endocrinology
Section
5. NHI-570
Serial No.
6. Determinants of the Renal Transport Process(es) for Aromatic Carboxylic Acids
Project Title
7. Agamemnon Despopoulos, M. D.
Principal Investigator(s)
8. None
Other Investigator(s)
9. PROJECT DESCRIPTION:

Project: Determinants of the Renal Transport Process(es) for Aromatic Carboxylic Acids.

Objectives: The object of this study is to develop a better understanding of the fundamental cellular processes with the end result of defining the mechanisms whereby cellular energy is translated into cellular work.

Methods Employed: Equipment and techniques have been tested for application to the desired purposes. Initial examination of the influences of salicylate ion and or uric acid on the accumulation of para-amino-hippurate (PAH) by slices of rabbit kidney cortex have have yielded suggestive data.

Major Findings: Sufficient information to permit definitive statements has not yet been accumulated; however, there are indications that both salicylate ion and uric acid depress the ability of the rabbit kidney cortex to concentrate PAH. This is associated with an increase in the respiratory rate of the tissue in the case of salicylate and with no change in this rate in the case of uric acid.

Significance to Heart Research: Through the understanding of the fundamental cellular processes it is hoped that the mechanisms whereby cellular energy is translated into cellular work will be elucidated.

Proposed Course of Project: These findings will be examined in vivo and in vitro.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-57
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 14,000	1	1	2	1.0	1.0	2.0	0
FY 1956	\$ 14,000	1	1	2	1.0	1.0	2.0	0

12. Budget Activity:

Research Administration
Review & Approval Technical Assistance

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-570
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute 2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Experimental Therapeutics Section 5. NHI-58C Serial No.
6. Effect of Exercise on Cardio-Respiratory Function in Patients with Cardiac Enlargement and/or "Heart Failure"
Project Title
7. Frank London, M. D.
Principal Investigator
8. None
Other Investigator(s)

9. PROJECT DESCRIPTION:

Project: The effect of exercise on cardio-respiratory function in patients with cardiac enlargement and/or heart failure.

Objectives: The object of this study is to develop an accurate method to quantify cardiac reserve which can be used both for clinical and investigative studies.

Methods Employed: Pilot runs have been done using all types of exercise. Low oxygen breathing mixtures have also been tried.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult Males	20	30
Adult Females	3	30
Outpatient: Number of Patients	6	
Number of Visits	12	

Major Findings: So far there has been no clear-cut separation of the abnormal from the normal response and we have begun to abandon the usual sub-maximal non-steady state response on the treadmill. It appears that there may be an increase in vital capacity with exercise in heart failure -- but we are not yet certain.

Significance to Heart Research: This study is significant to heart research in that it represents an attempt to develop an accurate method to quantify cardiac reserve which can be used both for clinical and investigative studies.

Proposed Course of Project: We plan to continue both a large number of pilot runs using all types of exercise and ones in which low oxygen breathing mixtures are used.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-58C
Serial No.

11. Budget Data:

	: Estimated : Expenditures	: Positions			: Man Years			: Patient : Days
		: Prof	: Other	: Total	: Prof	: Other	: Total	
FY 1955	: \$17,000	: 2	: 1	: 3	: 2.00	: 1.00	: 3.00	: 1000
FY 1956	: \$17,000	: 2	: 1	: 3	: 2.00	: 1.00	: 3.00	: 1100

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NHI-58C
Serial No.

16. None

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NHI-59C
Serial No.
6. Right Ventricular Function in Heart Disease
Project Title
7. Robert P. Grant, M. D.
Principal Investigator
8. None
Other Investigator
9. PROJECT DESCRIPTION:

Project: The determination of the function of the right ventricle in heart disease.

Objectives: The availability of simultaneous two-plane angio-cardiographic equipment and left atrial pressure measurements in bronchoscopic techniques made it likely that more precise information could be gained regarding chamber function in heart disease. Close collaboration with the surgical section has been indispensable for these studies.

Methods Employed: Cases of mitral valve disease have been the primary object of study. Calculations of right and left atrial volumes have been compared with left atrial and pulmonary artery pressures in mitral stenosis and insufficiency. In addition, observations have been made, the directions of motion of the various parts of the heart cycle in these subjects. Correlations with anterior chest motion has been attempted using a simple lever-and-air diaphragm technique.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions: Number adult males	6	7
adult females	6	7
Outpatient: Number of patients	0	

Major Findings: It has been found that the duration of exposure for each film in the angio is too long to capture events during systole, but are reliable during diastole. Accordingly only crude estimates of the

R.P.C. - 1
December 1954
NHI-59C

Major Findings: (continued)

sequences of motion during systole have been possible. The anomalous geometry of the right ventricle has made calculation of its volume impossible from two rectangular films. This has been a disappointment and studies of right ventricular events have been confined to measuring certain major axes.

The studies have been useful in studying some of the factors behind the "giant left atrium" syndrome and the properties of filling of the left and right ventricles in the presence of atrial fibrillation. It is planned to pursue this aspect of the findings further using other techniques.

Significance to Heart Research: This study has served to quantitate, perhaps already known, clinical suppositions regarding right ventricular function in heart disease.

Proposed Course of Project: It is doubtful if this project will be continued much further. This type of angiocardiology does not lend itself as satisfactorily as was hoped to physiological investigations and fluoroscope-intensified cine studies would appear to be more useful a technique not at present available.

However, the aspect of the factors behind the "giant left atrium" syndrome and the properties of filling of the left and right ventricles in the presence of atrial fibrillations will be pursued.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-59C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 7,000	2	2	4	.67	.83	1.50	1000
FY 1956	\$ 7,000	2	2	4	.67	.83	1.50	1100

12. Budget Activity:

Research	<input checked="" type="checkbox"/>	Administration	<input type="checkbox"/>
Review & Approval	<input type="checkbox"/>	Technical Assistance	<input type="checkbox"/>

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-59C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NHI-60C
Serial No.
6. Characteristics of Electrical Forces of QRS Complex in Bundle-Branch Block
Project Title
7. Harold T. Dodge, M. D. and Robert P. Grant, M. D.
Principals Investigator(s)
8. None
Other Investigator(s)
9. PROJECT DESCRIPTION:

Project: Characteristics of Electrical Forces of QRS Complex in Bundle-Branch Block.

Objectives: It is anticipated that by examination of large numbers of electrocardiographic records from patients who have records with QRS complexes of normal duration and who subsequently or intermittently get QRS prolongation, further insight will be gained as to the characteristics of such abnormalities. This should lead to a better understanding of the various types of QRS prolongation.

Methods Employed: Data have been collected from a number of other hospital electrocardiographic files and, at present, are being analyzed.

Major Findings: In certain patients with right bundle-branch block there seems to be isolated QRS activity over the anterior chest. This has been further pursued by recording "strips" in a number of patients with bundle-branch block.

Significance to Heart Research: This study represents an attempt to investigate, in the intact human, some aspects of the regulation of stroke volume of the heart, particularly its relationship to diastolic size of the heart.

Proposed Course of Project: It is proposed to analyze the data collected to date.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-60C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$8,000	3	2	5	1.17	1.00	2.17	1000
FY 1956	\$8,000	3	2	5	1.17	1.00	2.17	1100

12. Budget Activity:

Research Administration
Review & Approval Technical Assistance

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-60C
Serial No.

16. None.

17. None.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NHI-61C
Serial No.
6. Study of the Ventricular Dynamics in Pulsus Alternans and Auricular Fibrillation
Project Title tion
7. Harold T. Dodge and Fred T. Kirkham, M. D.
Principal Investigator(s)
8. None
Other Investigator(s)
9. PROJECT DESCRIPTION:

Project: The study of the ventricular dynamics in pulsus alternans and auricular fibrillation.

Objectives: The objective of this study is to better define the dynamics of ventricular contraction in the above conditions. From previous experimental and clinical data it is known that both conditions are associated with varying degrees of ventricular filling. It is hoped that through this study a better understanding of ventricular ejection characteristics under situations of variable ventricular filling will be forthcoming.

Methods Employed: Electrocardiograms of the left cardiac border have been recorded in patients with auricular fibrillation and varying ventricular response as well as in patients with pulsus alternans and multiple premature contractions. These curves have been treated as a qualitative index of cardiac volume and as such have been correlated with simultaneous recordings of carotid pulse, electrocardiogram, and direct brachial arterial pressure.

Patient Material: (calendar year 1954)

	<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions: Adult Males	22	1
Adult Females	9	1
Outpatient: Number of patients	23	
Number of visits	31	

Major Findings: From studies to date it appears that volume of ejection is related directly to the end-diastolic volume, irrespective of the RR interval. The end-diastolic volume is determined not only by the RR interval (filling time) but also by the preceding end-systolic size and the character of the filling curve. It appears that these hemodynamic factors largely control the variations in volume of ejection and that the nebulous factor of "recovery time" of myocardial fibers has often been invoked unnecessarily.

Significance to Heart Research: This is an attempt to further clarify ventricular function difficulty in human electrocardiograms.

Proposed Course of Project: In pulsus alternans, especially, further patient studies by our present techniques are necessary. In auricular fibrillation further efforts to obtain intraventricular pressure data are being made along lines noted above. Information about heart size during auricular fibrillation may be most helpful if a Phillips tube can be obtained for use with motion-picture recording. Discussions are being held with Doctor Sarnoff about the possibilities of confirming some features of this work through hemodynamic study on dogs.

R.P.C. - 2
December 1954

Analysis of NII Program Activities

Budget Data Sheet

10. NII-61C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$12,000	2	2	4	1.50	.83	2.33	750
FY 1956	\$12,000	2	2	4	1.50	.83	2.33	750

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

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December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-61C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NHI-62C
Serial No.
6. Non-Myocardial Contributions to the QRS Complex
Project Title
7. Robert P. Grant, M. D.
Principal Investigator
8. None
Other Investigator(s)

9. PROJECT DESCRIPTION:

Project: Non-myocardial contributions to the QRS Complex.

Objectives: To determine whether the high incidence of terminal R waves in lead V-1 in atrial septal defect and its rarity in other syndromes with right ventricular hypertrophy is due to high flow rates in the pulmonary artery creating a sort of streaming potential.

Methods Employed: In dogs it has been shown that the thrust of the pulmonary artery in systole produces a terminal R deflection in a lead obtained from the surface of this vessel if the electrode is held stationary, but is not present if the electrode rides with the pulmonary artery. Thus, the possibility of a non-myocardial contribution to the QRS complex has been proven.

Significance to Heart Research: The mechanism of a non-myocardial contribution to the QRS complex in animals has been proven. We are awaiting the opportunity to test this on humans.

Proposed Course of Project: The fact that this actually takes place in the human depends upon making similar tracings during cardiac surgery in a patient with such terminal R waves. The opportunity to do this has not yet arisen.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-62C
 Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$5,000	1	2	3	.33	.34	.67	365
FY 1956	\$5,000	1	2	3	.33	.34	.67	500

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-62C
SERIAL NO.

16. None

17. None

R.F.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NHI-63C
Serial No.
6. Relationship of the Elastic Properties of the Lung and Thoracic Cage to the Pulmonary Vascular Pressure.
Project Title
7. Donald L. Fry and Ben V. Branscomb, M. D.
Principal Investigators
8. None
Other Investigators

9. PROJECT DESCRIPTION:

Project: The study of the relationship of the elastic properties of the lung and thoracic cage to the pulmonary vascular pressure.

Objectives: The objective of this study is the establishment of methods of more accurate evaluation in cardiac function so that more subtle changes may be quantitated through observation and study of the mechanics of pulmonary function.

Methods Employed: The problem of dyspnea in congestive heart failure is almost certainly related to the altered mechanical properties of the pulmonary system in this disease. This experiment is designed to measure simultaneously the mechanical variables of the respiratory system in dogs. Simultaneously, the mechanical variables of pulmonary intravascular pressure, intrathoracic pressure, and "relaxation" pressure of the chest wall will be measured at various levels of intravascular pressure.

Major Findings: Preliminary studies indicate that acute pulmonary hypertension produces enlargement of the chest cage volume, decrease in the lung-gas volume, and increase in lung retractive force.

Significance to Heart Research: Studies in the mechanics of pulmonary function will be done to establish other methods of more accurate evaluation of cardiac function so that more subtle changes may be quantitated in animals.

Proposed Course of Project: In addition to developing methods of more accurate evaluation of cardiac function, a preparation in which the living lung can be temporarily made bloodless is being investigated.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-63C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 12,000	2	2	4	.83	.67	1.50	1000
FY 1956	\$ 12,000	2	2	4	.83	.67	1.50	1200

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-63C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Cardiodynamics Section
5. NHI-64C Serial No.
6. Evaluation of Cardiac Reserve in Human Subjects as Reflected by Alterations In Lung Elasticity and Resistance to Gas Flow.
Project Title
7. Donald L. Fry, M. D. and Ben V. Branscomb, M. D.
Principal Investigators
8. None
Other Investigators

9. PROJECT DESCRIPTION:

Project: To evaluate cardiac reserve in human subjects as reflected by alterations in lung elasticity and resistance to gas flow.

Objectives: The purpose of this study is to determine at which level of "cardiac reserve" these changes become apparent. It is hoped that these alterations of pulmonary function may reflect embarrassment of cardiac reserve not detectable by conventional means.

Methods Employed: Working in conjunction with the National Instrument Laboratories an electromechanical system was devised to maintain constant gas volume in a patient spirometer system. A thermal conductivity cell senses the concentration of a tracer gas -- helium. Any change of concentration is thereby converted to an electrical impulse through a servo-mechanism which admits oxygen to the spirometer. In this way the metabolic needs of the subject are constantly met in spite of wide variations in oxygen consumption.

Major Findings: Previous studies have shown that the elastic properties of the lung and the resistance to gas flow are markedly altered in cardiac decompensation. "Pilot" studies in dogs are in progress to gain preliminary information for this study.

Contribution to Heart Research: Studies in the mechanical and pulmonary function will be done to establish other methods of more accurate evaluation in cardiac function so that more subtle changes may be quantitated in man.

R. P. C. - 1
December 1954
NHI-64C (Ctd.)

Proposed Course of Project: Instruments for this study are being calibrated, and it is planned to proceed with the pilot studies in dogs and to carry these studies to the clinical level when patients become available.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-64C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 17,000	2	3	5	.50	1.83	2.33	750
FY 1956	\$ 17,000	2	3	5	.50	1.83	2.33	1000

12. Budget Activity:

Research	<input checked="" type="checkbox"/>	Administration	<input type="checkbox"/>
Review & Approval	<input type="checkbox"/>	Technical Assistance	<input type="checkbox"/>

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-64C
Serial No.

16. None

17. None.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NHI-650
Serial No.
6. Evaluation of Recording Characteristics of Modern Pressure Gage-Catheter Sys-
tems.
Project Title
7. Donald L. Fry, M. D.
Principal Investigator
8. None
Other Investigators
9. PROJECT DESCRIPTION:

Project: The evaluation of the recording characteristics of modern pressure gage-catheter systems.

Objectives: A comprehensive evaluation of the stability, static accuracy, and dynamic accuracy of the many combinations of catheters and physiologic pressure gages that are commonly used will be done. This will furnish a reference data to be used in future experimental design. An investigator will then simply need to refer to this data to choose the particular pressure recording system for his specific study.

Methods Employed: The equipment for the dynamic response studies has been devised and tested with satisfactory results. A few catheter manometer systems have been tested.

Major Findings: A new type of strain gage (P23) built by Statham Laboratories has been found to be a very excellent type of pressure recording device.

Significance to Heart Research: The establishment of static and dynamics of various pressure and recording systems in physiological studies.

Proposed Course of Project: This project awaits the arrival of further equipment for testing.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-650
 Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$ 6,000	2	1	3	.33	.34	.67	0
FY 1956	\$ 6,000	2	1	3	.33	.34	.67	0

12. Budget Activity:

Research

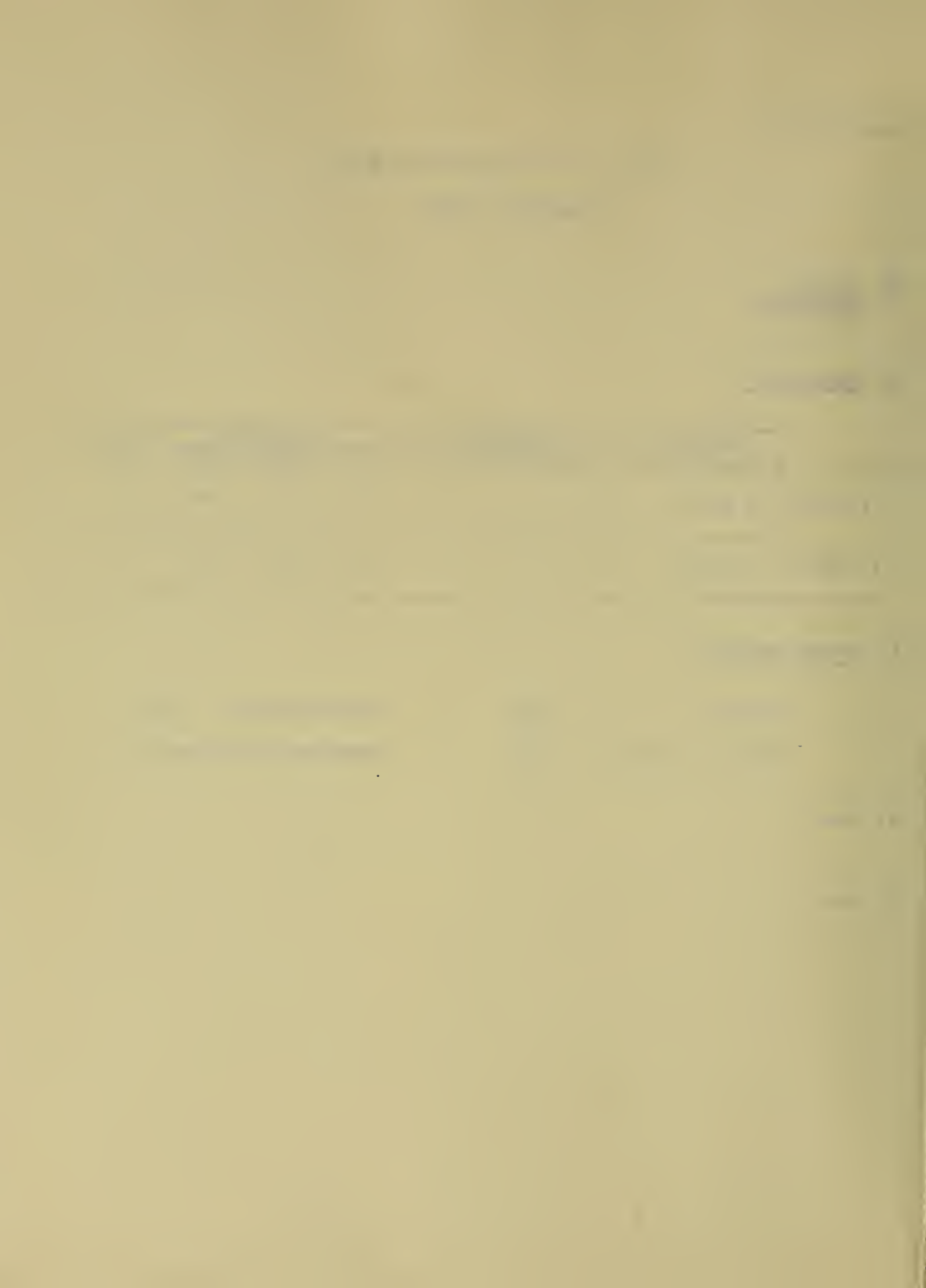
Administration

Review & Approval

Technical Assistance

13. None.

14. None.



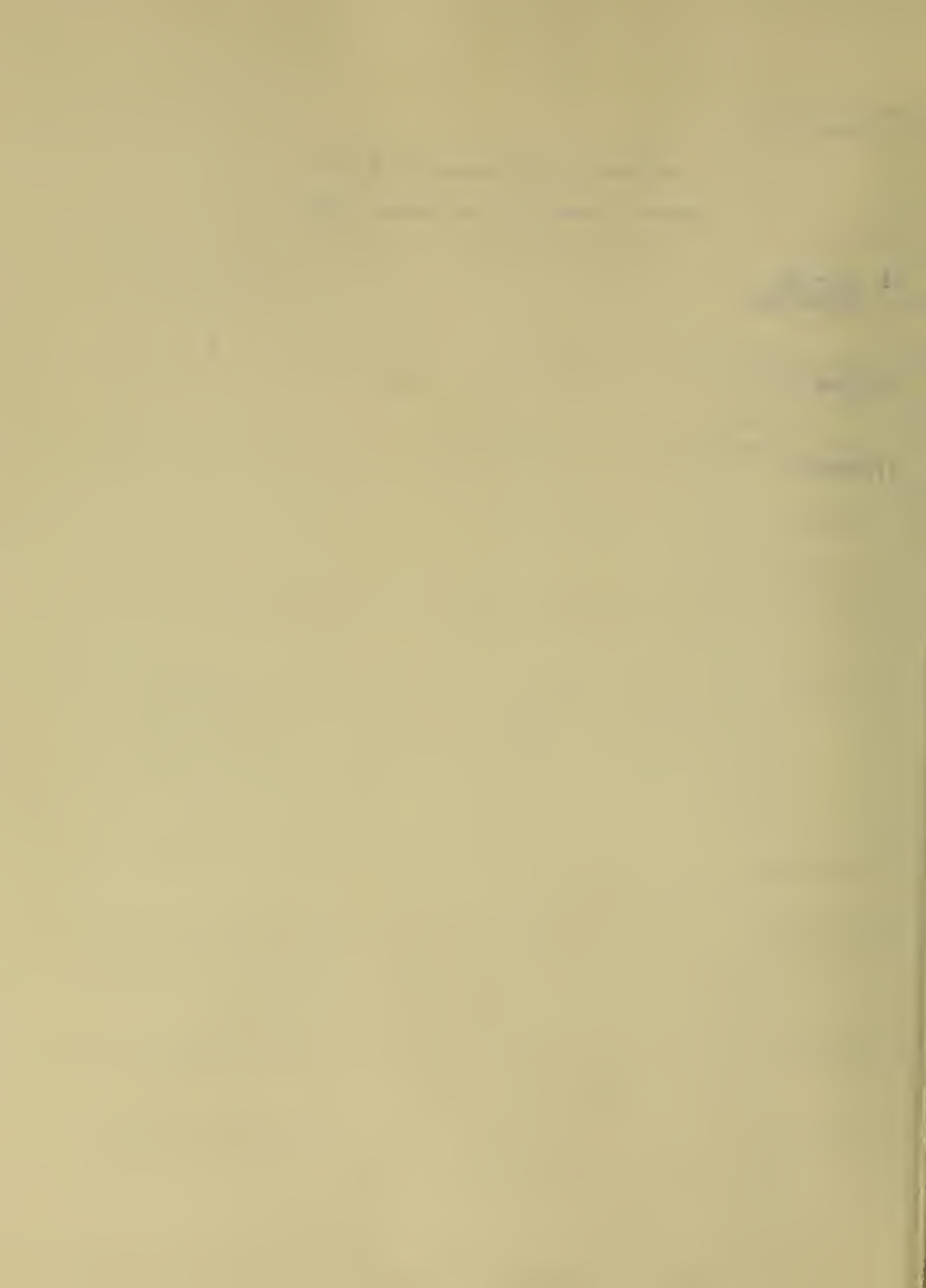
R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-658
Serial No.

16. None.

17. None.



R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
Institute
2. Clinic of General Medicine and Experimental Therapeutics
Laboratory or Branch
3. Cardiodynamics
Section
5. NIH-668
Serial No.
6. Evaluation of Cardiac Reserve in Dogs as Reflected by the "Time Power" Curve of the Heart.
Title of Project
7. Donald L. Fry, M. D.
Principal Investigator
8. None
Other Investigator(s)

9. PROJECT DESCRIPTION:

Project: The evaluation of cardiac reserve in dogs as reflected by the "time power" curve of the heart.

Objectives: Since the heart may be looked upon as a pumping engine from a purely functional point of view, its performance will be evaluated in a manner like its mechanical analogy. The power output will be determined using hydrodynamic and mechanical principles. Under conditions of progressively increasing stress, the power output of the heart will increase to its ultimate limit. This limit will be a measure of cardiac reserve. It is hoped that these animal studies will lend to a practical method of applying their principles to the human heart.

Methods Employed: The power output of the heart of the dog is determined using hydro-dynamic and mechanical principles.

Major Findings: The most formidable problem in this project has been the development of a satisfactory method of measuring blood flow. The use of the Pitot tube and orifice meter have been evaluated and found not entirely satisfactory. Progress on this study has temporarily halted pending purchase of the proper cinefluorographic instruments.

Significance to Heart Research: Animal studies will be done in which the power output of the heart will be measured directly in an attempt to more accurately assess cardiac function.

Proposed Course of Project: It is proposed to further extend the animal studies by a method of injecting small radio-opaque stream markers which may be followed by cinefluorographic technique.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-668
 Serial No.

11. Budget Data:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$ 9,000	2	2	4	.33	.85	1.17	0
FY 1956	\$ 12,000	3	3	6	.83	1.17	2.00	0

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. NHI-660
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Experimental Therapeutics Section
5. NHI-67C Serial No.
6. Evaluation of MCh112 (2-diethylaminoethylisonicotinamide) in the Treatment of Cardiac Arrhythmias
Project Title
7. Albert Sjoerdsma, M. D. and Thomas D. Stevenson, M. D. Principal Investigators
8. Julius Axelrod, Ph.D. Other Investigator(s)

9. PROJECT DESCRIPTION

Project: The evaluation of MCh112 (2-diethylaminoethylisonicotinamide) in the Treatment of cardiac arrhythmias.

Objectives: Animal experiments on this pronestyl-like compound have shown promise of its possible use in the treatment of cardiac arrhythmias in humans and certain advantages over procaine amide (pronestyl) as regards toxicity. It was deemed of interest to test the clinical effectiveness of this drug.

Methods Employed: Fifteen patients with cardiac arrhythmias of various types were given MCh112 intravenously.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	7	30
Adult females	8	30
Outpatient: Number of patients	10	
Number of visits	12	

Major Findings: There was no significant degree of antiarrhythmic action.

Significance to Heart Research: To evaluate drugs similar to pronestyl in the treatment of cardiac arrhythmia.

Proposed Course of Project: This study is nearing completion and it is planned to discontinue the study in 1955.

R.F.C. - 2
December 1954

Analysis of NIH Program Activities
Budget Data Sheet

10. NHI-67C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof.	Other	Total	Prof.	Other	Total	Days
FY 1955	\$5,000	3	1	4	.33	.34	.67	750
FY 1956	- 0 -	-	-	-	-	-	-	

12. Budget Activity:

Research

Administration

Review & Approval

Technical Assistance

13. None

14. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publication Sheet

15. NHI-67C
Serial No.

16. None

17. None

R.P.C.-1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Experimental Therapeutics Section
5. NHI-68C Serial No.
6. Pressor Substances Project Title
7. Albert Sjoerdsma, M. D. and Thomas D. Stevenson, M. D. Principal Investigator(s)
8. Bernard J. Haverback, M. D., Leroy E. Duncan, Jr., M. D. and Sidney Udenfriend, Ph.D. Other Investigator(s)
9. PROJECT DESCRIPTION:

Project: Pressor substances - Possible relation to blood pressure control.

Objectives: The object of this study is to study the various aspects of pressor substances and their possible relationship to blood pressure control.

Methods Employed: In the study of catechol amines two media have been explored:

1. Detection in urine. Using the extraction method of Goldenberg (Am. J. Med. 16:310, 1954) and the fluorimetric assay of Lund (Acta Pharmacol. 6:137, 1954), we have been able to achieve no more than 40 per cent recovery of known amounts of epinephrine added to urine. Contact with other people in this field suggests that current methodology is inadequate when applied to urine.

2. Detection in blood. The method of Weil-Malherbe and Bone (Biochem. J. 51:311, 1952) has been used successfully on human blood (e.g. Manger et al., Circulation 10:641, 1954). It is our plan to begin to develop this method in the Heart Institute both as a diagnostic (pheochromocytoma) and experimental tool.

The metabolism of Tyramine and Serotonin have also been studied: Studies were carried out on the metabolism of two pressor amines, Tyramine and Serotonin (5-hydroxytryptamine), by the use of the amine oxidase mechanism in rat and rabbit tissue homogenates.

Patient material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	3	30
Adult females	2	30
Outpatient: Number of patients	12	
Number of visits	15	

Major Findings: The similarity of Serotonin metabolism to that of Tyramine and the inhibition of the metabolism of these agents by Marsilid (isopropyl derivative of nicotinic acid, a specific inhibitor of amine oxidase) implicates the amine oxidase mechanism for both of these agents.

Significance to Heart Research: This study represents the evaluation of metabolism of naturally occurring pressor agents and their role in human high blood pressure.

Proposed Course of Project: Further development of the method of detection in blood (under heading of Catechol Amines) is planned.

Although no further studies are planned with Tyramine and Serotonin metabolism, it is of interest that Marsilid may be given to patients for short periods of time with impunity. A unique syndrome has recently been described by Thorson et al. (Am. Heart J. 47:795, 1954) of cardiovascular alterations in the presence of malignant carcinoid. Large amounts of Serotonin are produced by this tumor. A patient with this syndrome was recently admitted to the Clinical Center for extensive metabolic studies.

Recent experimental data show that cross perfusion of blood from a renal hypertensive animal induces a rise in blood pressure in a salt-loaded - but not in a normal - animal. Certain implications of this finding will be explored with Dr. Leroy E. Duncan, Jr. and Dr. Robert Akers.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-68C
 Serial No.

11. Budget Data:

	Estimated Expenditures	Positions			Man Years			Patient Days
		Prof.	Other	Total	Prof.	Other	Total	
FY 1955	\$11,000	5	1	6	1.17	.33	1.50	750
FY 1956	\$15,000	6	1	7	1.67	.33	2.00	850

12. Budget Activity:

- Research
- Administration
- Review & Approval
- Technical Assistance

13. None.

14. None.

R.P.C.- 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NIH-68C
Serial No.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Experimental Therapeutics Section
5. NHI-69C Serial No.
6. Evaluation of the Gastrointestinal Effects of Two Anti-Hypertensive Drugs
Project Title
7. Bernard J. Haverback, M. D.
Principal Investigator(s)
8. Thomas D. Stevenson, M. D. and Albert Sjoerdsma, M. D.
Other Investigators
9. PROJECT DESCRIPTION:

Project: Evaluation of the Gastrointestinal Effects of Two Anti-Hypertensive Drugs.

Objectives: The gastrointestinal effects of Reserpine and Chlorpromazine are being studied. Reserpine in animal experimentation has been shown to increase gastric acid secretion and also to increase intestinal motility. The purpose of this research is to determine these effects in humans and to determine whether they will bring about untoward gastrointestinal reactions. Chlorpromazine has been shown to decrease gastric acid secretion in animal experimentation. Our purpose is to determine whether this applies to the human and how effective it is in this regard.

Methods Employed: Selected patients with hypertension are being carried on these drugs and the effects of the drugs on the gastrointestinal tract are being recorded and evaluated.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult Males	60	15
Adult Females	48	15
Outpatient: Number of Patients	1	
Number of Visits	4	

Major Findings: Preliminary studies in humans have shown that Reserpine increases both the volume and degree of free acid of gastric secretion and increases motility of the colon. Early studies on Chlorpromazine in humans show that this drug decreases gastric acidity and decreases gastric motility.

R.P.C. - 1
NHI-69C (Continued)

Significance to Heart Research: Reserpine and Chlorpromazine are being widely used in clinical medicine and in the field of cardiology. However, no basic data concerning their effects on the gastrointestinal tract have been established. It is our plan to develop a basic working knowledge of the gastrointestinal effects of the drugs.

Proposed Course of Project: It is planned to extend and continue the above studies.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-69C
Serial No.

11. Budget Data:

	Estimated	Positions			Man Years			Patient
	Expenditures	Prof	Other	Total	Prof	Other	Total	Days
FY 1955	\$9,000	3	0	3	1.17	0	1.17	750
FY 1956	\$9,000	3	0	3	1.17	0	1.17	?

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of the NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-690
Serial No.

16. None.

17. None.

R.P.C. = 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart Institute
2. Clinic of General Medicine and Experimental Therapeutics Laboratory or Branch
3. Experimental Therapeutics Section
5. NHI-70C Serial No.
6. Evaluation of Andromedotoxin in Human Hypertension Project Title
7. Thomas D. Stevenson, M. D., Albert Sjoerdsma, M. D., and Luther L. Terry, M. D.
8. None Other Investigator(s)

9. PROJECT DESCRIPTION:

Project: The Evaluation of Andromedotoxin in Human Hypertension.

Objectives: The evaluation of the effectiveness of Andromedotoxin as an anti-hypertensive agent.

Methods Employed: A large series of patients with hypertension has been studied under conditions of slow intravenous infusion of Andromedotoxin.

Patient Material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult Males	20	30
Adult Females	20	30
Outpatient: Number of patients	56	
Number of visits	83	

Major Findings: It has been clearly shown that Andromedotoxin does have anti-hypertensive effects in humans and that under careful observation the blood pressure levels can be accurately controlled during constant intravenous infusions. Furthermore, it has been shown that atropine rapidly abolishes all of the effects of Andromedotoxin.

Significance to Heart Research: It is a great significance if a more satisfactory antihypertensive agent can be found than those now available. This would be particularly true if the substance could be administered by mouth and the results were fairly accurately predictable.

Proposed Course of Project: It is planned that Andromedotoxin will be used in clinical cases of severe hypertension. Under such circumstances, intravenous infusions will be the route of administration. It is expected that we will also explore the possibility of intramuscular administration of Andromedotoxin. It has already been demonstrated that this substance is largely destroyed by the gastric acids when administered by mouth. Enteric-coated pills have been prepared and administration in this manner will be tried in human beings.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-70C
Serial No.

11. Budget Data:

	: Estimated Expenditures :	: Positions :			: Man Years :			: Patient Days :
		: Prof. :	: Other :	: Total :	: Prof. :	: Other :	: Total :	
FY 1955	: \$12,000	: 3	: 1	: 4	: .83	: .34	: 1.17	: 2000
FY 1956	: \$12,000	: 3	: 1	: 4	: .83	: .34	: 1.17	: 2000

12. Budget Activity:

Research



Administration



Review & Approval



Technical Assistance



13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-700
Serial No.

16. None.

17. None.

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Cellular Physiology and Metabolism
5. SERIAL NO.: NHI-71
6. PROJECT TITLE: The enzymatic synthesis of energy-rich compounds and their utilization in biosynthetic reactions.
7. PRINCIPAL INVESTIGATOR: E. R. Stadtman
8. OTHER INVESTIGATORS: R. Brady, I. Harary (Postdoctoral fellows)
9. PROJECT DESCRIPTION:

Objectives: It is the object of this project to study those enzymatic reactions which lead to the formation of substances with high free energies of hydrolysis and to determine how the potential energy of such compounds is used to promote various biosynthetic reactions.

Methods employed: By means of the enrichment culture technique, microorganisms are selected whose metabolism is specifically concerned with the dissimilation of substances of particular biochemical interest. Cell-free extracts and purified enzyme preparations of these organisms are used to elucidate the biochemical mechanism of the metabolism of the various compounds. These studies are supplemented with similar studies using tissue extracts of animals.

Major findings: It has been demonstrated that cell-free extracts of bacteria and pigeon liver extracts contain enzyme systems that catalyze a reversible transfer of the acyl-moiety of acyl coenzyme A to various mercaptans. Since thioesters are in the class of so-called "energy rich" compounds, these enzyme systems provide one mechanism by which metabolic energy trapped in the form of acyl coenzyme A derivatives may be transferred, without loss, to form other thioesters which may be more direct precursors in the synthesis of specific compounds.

Microorganisms which catalyze the decomposition of riboflavin have been obtained in a partially purified state. Lumichrome and 6,7-dimethyl-9-(2'-hydroxyethyl) iscalloxazine have been identified among the products of riboflavin decomposition by these organisms.

Significance to Heart Research: This project is part of the basic research program of the Heart Institute and although there is no immediate obvious relationship to heart disease, this research will result in the accumulation of fundamental information on one of the more important aspects of intermediary metabolism; namely, that concerned with the biochemical mechanism of deriving chemical energy from food materials and the utilization of this energy for the maintenance and synthesis of cellular constituents. Such information will undoubtedly lead eventually to a better understanding of heart metabolism and degenerative diseases.

Project Description Sheet Continued - NHI 71

The isolation of 6,7-dimethyl-9-(2' hydroxyethyl) isoalloxazine (ethanol flavin) as a major end product of riboflavin degradation by anaerobic microorganisms is of incidental interest to cancer research since this compound shows promise as an effective therapeutic agent in the treatment of certain forms of cancer.

Proposed course of project: The above studies will be continued. Much time will be devoted to the study of the enzymatic mechanism of riboflavin degradation and the degradation of other related nitrogen compounds.

Analysis of NIH Program Activities
Budget Data Sheet

10. SERIAL NO.: NHI-71

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 19,500	3	2	5	1	1.33	2.33	--
FY 1956	20,000	1	2	3	1	2.33	3.33	--

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THE PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1):

American Cancer Society made available a postdoctoral research fellowship to Dr. Isaac M. Harary to work in this laboratory as a guest scientist.

14. None.

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. SERIAL NO.: NHI-71

16. PUBLICATIONS:

On the Energy-Rich Nature of Acetyl Imidazole, an Enzymatically Active Compound, "The Mechanism of Enzyme Action", edited by William D. McElroy and Bentley Glass. The Johns Hopkins Press, Baltimore, 1954.

Studies on the Biochemical Mechanism of Fatty Acid Oxidation and Synthesis, Vol. 15, No. 1, 1954 "Record of Chemical Progress", Copyright 1954 by Friends of the Kresge-Hooker Scientific Library

The Role of Sulfhydryl Compounds in Acyl Transfer Reactions, Symposium on Glutathione, Academic Press (1954)

Discussions in Symposium on Glutathione, Academic Press (1954)

A Resin for the Selective Retention of Sulfhydryl Compounds (with H. T. Miles and W. W. Kielley), J. Am. Chem. Soc. 76, 4041

Enzymatic Thioltransacetylation (with R. O. Brady), J. Biol. Chem. 211, 621(1954).

Thiol-thiolester Complex Formation (with W. W. Kielley and L. B. Bradley), Symposium on Glutathione, Academic Press, p. 57 (1954)

Amino Acid Metabolism, Science, vol. 120, 589 (1954).

In Press:

Aldehyde Dehydrogenase from Clostridium kluyveri (with R. M. Burton), Methods in Enzymology, Academic Press.

Coenzyme A Transphorase from Clostridium kluyveri (with H. A. Barker and A. Kornberg), ibid.

Phosphotransacetylase from Clostridium kluyveri, ibid.

17. HONORS AND AWARDS. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Cellular Physiology and Metabolism
5. SERIAL NO.: NHI-72
6. PROJECT TITLE: The enzymatic conversion of serine to glycine
7. PRINCIPAL INVESTIGATOR: Barbara Wright Kalckar
8. OTHER INVESTIGATORS: None
9. PROJECT: The enzymatic conversion of serine to glycine.

Objectives: To determine the biochemical mechanism by which serine is converted to glycine.

Methods employed: Cell-free extracts capable of catalyzing the biosynthesis of glycine from serine are prepared from an anaerobic bacterium Clostridium HF. These extracts are subjected to enzymological analysis in order to establish the nature of the chemical reactions involved in glycine formation.

Major findings: It has been determined that in addition to various protein catalysts, the formation of glycine from serine involves the participation of the following coenzymes and cofactors: diphosphopyridine nucleotide (DPN), orthophosphate, pyridoxal phosphate, manganese (Mn^{++}), and a heat-stable, unidentified coenzyme which may be derived from various bacterial and tissue extracts. The latter coenzyme has been extensively purified and chemical tests indicate that it is a folic acid derivative. It has been shown that the conversion of serine to glycine involves the simultaneous formation of formic acid and other as yet unidentified one-carbon derivatives.

Significance to Heart Research: Results of isotopic tracer studies have revealed that one-carbon compounds or activated derivatives thereof play a key role in intermediary metabolism. The present research project, as a part of the fundamental research program of the Heart Institute, is directed toward the accumulation of basic information in this general area of biochemistry. Since it is established from tracer studies that the conversion of serine to glycine is associated with the formation of an active one-carbon compound, a detailed study of this reaction will supply important information on the chemical nature of the as yet unidentified active one-carbon precursors and will help to establish the mechanism by which these compounds are used in biosynthetic reactions. Such information should lead ultimately to a better understanding of heart metabolism and of intermediary metabolism in general.

Proposed Course of Project: The above investigation will be continued. Attempts will be made to isolate the folic acid containing coenzyme in pure form and to establish its chemical composition. The protein fraction of cell-free extracts of Clostridium HF will be further fractionated in order to help establish the individual steps involved in the over-all conversion of serine to glycine.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Cellular Physiology and Metabolism
5. SERIAL NO.: NHI-72
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Proposed Course of Project: The above investigation will be continued. Attempts will be made to isolate the folic acid containing coenzyme in pure form and to establish its chemical composition. The protein fraction of cell-free extracts of Clostridium HF will be further fractionated in order to help establish the individual steps involved in the over-all conversion of serine to glycine.

R.P.C. 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI-72

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 8,600	1	0	1	1	0	1	--
FY 1956	8,600	1	0	1	1	0	1	--

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

15. SERIAL NO.: NHI-72

16. PUBLICATIONS:

Discussion in proceedings of "Symposium on Amino Acid Metabolism", Johns Hopkins Press, Baltimore, Md. (1954).

In Press: A New Cofactor in the Conversion of Serine to Glycine, Biochimica et Biophysica Acta.

17. HONORS AND AWARDS: None

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Cellular Physiology and Metabolism
5. SERIAL NO.: NHI-73
6. PROJECT TITLE: Muscle Proteins
7. PRINCIPAL INVESTIGATOR: W. Wayne Kielley
8. OTHER INVESTIGATORS: None
9. PROJECT: Muscle Protein

Objectives: To characterize further the proteins derived from the contractile elements of muscle with special reference to the physical and chemical nature of their reaction with adenosinetriphosphate and with the ultimate goal of understanding the mechanism of energy transfer in muscular contraction.

Methods employed: Elements of the contractile proteins of muscle are obtained by extraction with salt solutions and fractionated by varying the salt concentration. Enzyme activities are studied with standard techniques. Physical studies include viscosity measurements employing standard methods of double refraction of flow using an apparatus specially constructed for investigations of these proteins.

Particulate elements of tissue are isolated by established centrifugal methods. Studies on coupled oxidative phosphorylation are conducted on the intact particle or on fractions of the particles resulting from disintegration by a variety of techniques.

Major findings: It is now widely recognized that myosin ATP-ase may be activated by either calcium ions or ethylenediaminetetraacetic acid (EDTA), two reagents expected to be opposite in effect. It has been observed that activation of hydrolysis by EDTA is limited to purine or pyrimidine riboside triphosphates with a 6-amino group (adenosine and cytidine triphosphates) whereas the most active substrates with calcium ion as activator are the 6-hydroxy compounds (inosine and uridine triphosphate). The results indicate that the same enzyme is responsible for hydrolysis of all the substrates and that activation of a preliminary transfer from one to another is not an obligatory part of the mechanism of hydrolysis.

Activation by EDTA is markedly dependent on salt concentration and the nature of the cation present. Ammonium, potassium and rubidium salts activate the system whereas lithium and sodium salts are without effect.

It has been found that myosin and actomyosin possess two types of sulfhydryl groups relative to the catalysis of ATP hydrolysis with calcium ion as the activator. One group is essential for catalysis whereas the other exerts an inhibitory effect on hydrolysis. In the presence of EDTA the system appears to be relieved of the effect of the inhibitory group.

Project Description Sheet Continued - NHI-73

As evidenced by studies on double refraction of flow, these sulfhydryl groups are not primarily responsible for the binding of ATP by the protein nor do they appear to be involved in maintaining the structure of the elongated particles.

Significance to Heart Research: Muscular contraction is the main activity of the heart. The chemical energy needed to promote muscle activity is mainly "phosphate bond" energy which is derived from heart respiration. Therefore studies of the biochemistry of the contractile elements of muscle together with those processes leading to the generation of "phosphate bond" energy are basic to an understanding of heart mechanics. The present research project is directed toward the accumulation of fundamental information on these important biochemical processes.

Proposed course of project: 1. Muscle Protein. The present work on the mechanism of activation and the relationships of sulfhydryl groups to ATP-ase activity of myosin will be continued as well as studies on the physical changes induced in myosin solutions by ATP.

2. Oxidative phosphorylation. The relationships of transphosphorylases to oxidative phosphorylation will be pursued and a study of some model reactions of flavin enzymes will be initiated.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI-73

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 17,100	1	1	2	1	1	2	--
FY 1956	17,100	1	1	2	1	1	2	--

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

1880

1881

1882

1883

1884

1885

Analysis of NIH Program Activities
Honors, Awards and Publication Sheets

15. SERIAL NO. NHI-73

16. PUBLICATIONS:

The Enzymatic Hydrolysis of S-Acetyl and S-Butyryl Glutathione,
W. Wayne Kielley and Louise B. Bradley, Glutathione, A Symposium
Academic Press, N.Y. (1954)

Thiol-Thiolester Complex Formation, W. Wayne Kielley, E. R. Stadtman
and Louise B. Bradley, Glutathione, A Symposium, Academic Press, N.Y.
(1954)

Glutathione Thiolesterase, W. Wayne Kielley and Louise B. Bradley,
J. Biol. Chem. 206,327 (1954)

Biological Oxidations, Christian B. Anfinsen and W. Wayne Kielley,
Annual Review of Biochemistry 23, 17 (1954)

A Resin for the Selective Retention of Sulfhydryl Compounds,
H. T. Miles, E. R. Stadtman and W. W. Kielley, J. Am. Chem. Soc. 76,
4041 (1954)

In Press: Methods in Enzymology, A6 PHOSPHATASES, ATPases, Mg-activated muscle ATPases
A6 PHOSPHATASES, ATPASES, Mitochondrial ATPase, Johns Hopkins Press,
Baltimore, Maryland

17. HONORS AND AWARDS: NONE

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Cellular Physiology and Metabolism
5. SERIAL NO.: NHI-74
6. PROJECT TITLE: Studies on Heparin and Heparin-Activated Lipoprotein Lipase
7. PRINCIPAL INVESTIGATOR: Edward D. Korn
8. OTHER INVESTIGATORS: Nail Payza (postdoctoral fellow)
9. PROJECT: Studies on Heparin and Heparin-Activated Lipoprotein Lipase

Objectives: To study the properties of lipoprotein lipase and its role in fat transport and metabolism, also to clarify the function of heparin in the reaction catalyzed by this enzyme and to study the structure, biosynthesis and enzymatic degradation of heparin.

Methods employed: I. Purification and Properties of Lipoprotein Lipase. Fresh heart mince or acetone-dried powder of heart are extracted with dilute ammonia to obtain cell-free preparations. These extracts are studied using enzymological procedures to determine those factors which influence their ability to catalyze the hydrolysis of the triglyceride moiety of plasma and synthetic lipoprotein complexes.

II. Heparin metabolism. Microorganisms are being isolated by enrichment culture techniques which are capable of growing on heparin as the sole carbon source. Contemplated studies on the enzyme degradation of heparin by extracts of these organisms will provide information on the biochemistry and chemical structure of heparin.

Major findings: It has been discovered that rat heart extracts contain a specific lipoprotein lipase which catalyzes the hydrolysis of the triglyceride moiety of chylomicrons and related large lipoprotein complexes. In contrast to pancreatic lipase, this enzyme does not hydrolyze simple triglycerides. It is inhibited by inorganic pyrophosphate and by high salt concentrations, and it appears to require heparin as a specific co-enzyme or activator.

Simple triglycerides (in the form of coconut oil) which are not attacked by the enzyme are converted to enzymatically active chylomicrons by interaction with α - and β -lipoprotein fractions of normal serum. In addition, calcium ions or a protein (viz. albumin) must be present to bind the free fatty acids released as a result of the hydrolysis.

Comparative studies indicate that the heart enzyme system is probably identical with the lipemia clearing system found in the serum of heparin-treated animals.

Project Description Sheet Continued

Significance to Heart Research: It is currently believed by most investigators that atherosclerosis is the direct or indirect result of abnormal fat transport or metabolism. Since plasma lipids exist almost exclusively in the form of lipoprotein complexes, studies on the enzymatic mechanism of biosynthesis and degradation of these complexes are obligatory to the ultimate understanding of the phenomena of lipid transport and metabolism. Results of the present investigation demonstrating the existence and properties of a specific lipoprotein lipase in heart and in the serum of heparin-treated animals, constitute a direct contribution to our knowledge of these important processes, and provide an experimental basis for a new concept of lipid transport in which the α - and β -lipoproteins and the lipoprotein lipase are catalytic agents.

Since heparin appears to be a normal specific activator of this lipoprotein lipase, studies on the chemical behavior and structure of this substance will aid in evaluation of its role as a co-enzyme in lipid metabolism.

Proposed Course of Project: I. Purification and Properties of Lipoprotein Lipase. A major portion of our effort will be devoted to the purification of the enzyme from fresh calf heart. With the purified enzyme it will be possible to establish whether the enzyme contains bound heparin and to study other properties of the enzyme which cannot be done with the crude preparations.

Experiments will be done, in collaboration with Dr. D. Steinberg, to identify the protein moiety which remains when lipoprotein lipase removes the triglyceride from chylomicrons and β -lipoproteins.

II. Heparin Metabolism: It is hoped that one or more bacteria will be obtained in a pure form so that they can be grown in quantity as a source of enzymes which will degrade heparin. By the characterization of partial degradation products of heparin it may be possible to reconstruct the original molecule.

Analysis of NIH Program Activities

Budget Data Sheet

1. SERIAL NO. NHI-74

2. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$19,500	2	1	3	2	.33	2.33	-
FY 1956	19,500	2	1	3	2	.33	2.33	-

3. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

4. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1) -

Foreign Operations Administration Exchange Visitor - Scientist
Dr.Nail Payza

5. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI-74

16. PUBLICATIONS:

Properties of Clearing Factor Obtained from Rat Heart Acetone Powder, E. D. Korn, Science 120, 399 (1954)

Studies on Clearing Factor, A Lipoprotein Lipase, E. D. Korn, Circulation 10, 591 (1954)

In Press:

Biosynthesis of the Purines VI. Purification of Liver Nucleoside Phosphorylase and Demonstration of Nucleoside Synthesis from 4-Amino-5-imidazolecarboxamide, Adenine and 2,6-Diaminopurine, E. D. Korn and J. M. Buchanan, J. Biol. Chem.

Synthesis and Degradation of Labeled Purines and Pyrimidines, E.D. Korn, "Methods in Enzymology" by Colowick and Kaplan

Clearing Factor, A Heparin-Activated Lipoprotein Lipase. I Isolation and Characterization of the Enzyme From Normal Rat Heart, E. D. Korn, J. Biol. Chem.

Clearing Factor, A Heparin-Activated Lipoprotein Lipase. II Substrate Specificity and Activation of Coconut Oil, E. D. Korn, J. Biol. Chem.

17. Honors and Awards: None.

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Cellular
Physiology and Metabolism

SERIAL NO.: NHI - 75

PROJECT TITLE: 1. Role of glutathione as a precursor of the cysteinyl
glycine of ovalbumin
2. Structure and biosynthesis of phosphoproteins: sites
of phosphate linkage and sequences of neighboring amino
acids in ovalbumin and pepsin

PRINCIPAL INVESTIGATOR: Martin Flavin

OTHER INVESTIGATORS: None

PROJECT: 1. Role of glutathione as a precursor of the cysteinyl
glycine of ovalbumin
2. Structure and biosynthesis of phosphoproteins: sites
of phosphate linkage and sequences of neighboring amino
acids in ovalbumin and pepsin.

Objectives: The immediate objectives of the project are (1) to determine if glutathione is a more or less direct precursor of the cysteine, glycine and cysteinyl-glycine residues of ovalbumin; (2) to obtain basic information on the fine structure of ovalbumin and pepsin.

Methods employed: Glutathione, labelled with S^{35} and with C^{14} -glycine is incubated in vitro with oviduct preparations. The ovalbumin is isolated, treated with performic acid to oxidize the sulfhydryl groups. The oxidized protein is partially hydrolyzed and the cysteic acid and phosphate containing peptides are isolated by ion exchange chromatography. Amino acid sequences are determined by conventional methods and the isotope content of the cysteic acid and glycine moieties are compared. The nature of the phosphorylated peptides is examined by studies with specific phosphatase.

Major findings: Eleven of the 14 theoretically possible cysteine containing sequences in ovalbumin have been identified. Of these only one is cysteinyl-glycine.

From the experiment with isotopically labeled glutathione the isolation and determination of specific radioactivity of several different glycine and cysteine residues from specific sites along the ovalbumin chain gave results which do not support any special role for glutathione in the biosynthesis of cysteinyl-glycine sequences.

Results of studies on the phosphorylated proteins are interpreted to indicate that both phosphate residues of ovalbumin are linked to serine. One which is resistant to prostatic phosphatase has the sequence Aspartyl-phosphoseryl-glutamyl isoleucyl-alanine, and the other which is labile to the phosphatase is in the sequence Glutamyl-phosphoseryl-alanine. Dephosphorylation of ovalbumin was found not to unmask any N-terminal amino acids. The rapid biological turnover of phosphoprotein phosphorus was shown to be associated with a rapid turnover of any part of the peptide chain in ovalbumin. The phosphate residue of beef pepsin has been found to be present in the sequence Threonyl-phosphoseryl-glutamic acid.

Project Description Sheet Continued

Significance to Heart Research: This project is part of the basic research program of the Heart Institute and is designed to obtain fundamental information on the mechanisms of protein biosynthesis and enzyme action.

Since the sulfhydryl groups and probably phosphate groups also of protein molecules play important roles as sites of enzyme activity, the present investigations on the peptide sequences adjacent to these groups provide an opportunity to examine the amino acid configuration at the "active-centers" of enzymes. This kind of basic information will help in the ultimate understanding of the mechanism of enzyme action and at the same time, by adding our knowledge of the fine structure of protein molecules, will assist in the development of a reasonable approach to the problem of protein biosynthesis.

Proposed course of research: The above research projects were temporarily discontinued in February of last year when Dr. Flavin began some collaborative studies on a new project with Dr. Severo Ochoa at New York University, and when Dr. Anfinsen left the laboratory for a year's leave of absence last June. These projects will be continued when these persons return to the NIH next year.

Project: 3. β -ketothiolase from heart muscle: Properties and mechanism
4. Propionic acid metabolism in heart muscle.

Objectives: The objective of project 3 is to purify and study the properties of the enzyme β -ketothiolase. The objective of project 4 is to obtain information on the mechanism of the propionate-dependent CO_2 fixation reaction of heart muscle.

Major findings: Purified ketothiolase preparations from heart muscle are completely inhibited by 10^{-5} M iodoacetamide. This inhibition is completely reversed by preincubation with 2×10^{-3} M acetoacetyl CoA. 2×10^{-3} M acetyl CoA protects the enzyme 25% from iodoacetamide inhibition, 2×10^{-2} M glutathione protects 50%, and 10^{-1} glutathione protects completely. No protection is observed with CoA or acetic anhydride.

Extracts of washed pig heart muscle supplemented with propionyl CoA, ATP, Mg^{++} , and glutathione, were found to fix C^{14}O_2 into a non-volatile compound, at first identified by chromatography as succinic acid. Doubt as to the identity of the product was raised, however, by failure of C^{14} to appear in malate or fumarate after treatment of the labeled product with succinoxidase, and further studies have now led to the tentative identification of isosuccinic (methylmalonic) acid or a labile derivative as the product of the reaction in heart muscle extracts. This acid does not appear to have been previously described in nature, though it or similar compounds have recently been implicated in the degradative metabolism of thymine and valine.

The product of the reaction between the same components, propionyl CoA, C^{14}O_2 , and ATP, when catalyzed by dialyzed rat liver extracts has been found on the contrary, to be succinic acid, accompanied under some conditions by malic acid.

Project Description Sheet Continued

NHI-75

Significance to Heart Research: These projects are aimed at the accumulation of basic information on the intermediary metabolism of heart muscle.

Proposed Course of Research: Studies will be made on the possible metabolic relation between succinic and isosuccinic acids, and of the possible formation and transfer of an activated carbon dioxide in their synthesis and inter-conversion.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO. NHI-75

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 8,600	1	0	1	1	0	1	--
FY 1956	\$ 8,600	1	0	1	1	0	1	--

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

New York University supplying working space and facilities for 1955.

14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI-75

16. PUBLICATIONS:

The Linkage of Phosphate to Protein in Pepsin and Ovalbumin,
J. Biol. Chem. 210, 771 (1954)

Cysteine and Phosphoserine Containing Peptide Sequences of
Ovalbumin, Nature 173, 214 (1954)

The Isolation and Characterization of Cysteic Acid Peptides
in Studies on Ovalbumin Synthesis (with C. B. Anfinsen),
J. Biol. Chem., 211, 373 (1954)

17. HONORS AND AWARDS - None.

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Cellular
Physiology and Metabolism

SERIAL NO.: NHI-76

PROJECT TITLE: Synthesis, Isolation and Characterization of Compounds of
Biological Interest

PRINCIPAL INVESTIGATOR: H. Todd Miles

OTHER INVESTIGATORS: None

PROJECT: Synthesis, Isolation and Characterization of Compounds of
Biological Interest

Objectives: The purpose of this research is to synthesize compounds of special biochemical interest to be used as substrates in enzyme studies by other members of the Laboratory of Cellular Physiology. In addition substances accumulating as biological intermediates in studies on intermediary metabolism are isolated and identified.

Major Findings: A resin has been prepared by mercuration of a phenol-formaldehyde polymer that will selectively remove mercaptans from aqueous solutions. The mercaptans can be recovered by elution with dilute 2-mercaptoethanol or hydrogen sulfide solutions.

Experiments with cysteine, glutathione, and coenzyme A indicate that both retention and recovery are quantitative under the conditions used. The conditions necessary for elution indicate that coenzyme A is much more strongly retained than the other two compounds. Lysine, serine, and alanine were found not to be retained.

N-acetyl-S-crotonylmercaptoethylamine has been prepared for enzymatic study by W. W. Kielley. S-Acetyl-2-mercaptoethanol and N-acetylmercaptoethylamine have been prepared for enzymatic study by E. R. Stadtman. Tetrahydrofolic acid has been prepared for enzymatic study by B. W. Kalckar.

An anaerobic bacterial fermentation product of riboflavin has been identified as 6,7-dimethyl-9-(2'-hydroxyethyl) isocalloxazine. The acetyl derivative of this bacterial fermentation product has also been prepared.

The identity of the red and green substances formed from riboflavin in the bacterial cultures has been found to be quinhydrone-like complexes of half reduced flavins with either oxidized or fully reduced flavins. The bacterial fermentation product has been shown to undergo the same color changes as are observed in the bacterial cultures under appropriate conditions of chemical reduction, and to revert to the original yellow compound on air oxidation. A green substance isolated from one of the bacterial fermentations was air oxidized to a yellow compound and shown to be the same 6,7-dimethyl-9-(2'-hydroxyethyl)-isocalloxazine, isolated previously in the yellow, fully oxidized form.

Project Description Sheet - Continued - NHI-76

The structure and spectra of reduced riboflavin are being studied. It has been found that with a number of chemical reductants as well as with catalytic hydrogenation some care must be employed to avoid (irreversible) reduction beyond the dihydro stage. The most promising results so far have been obtained by reduction to constant ultraviolet spectrum with potassium borohydride, followed by decomposition of the borohydride with acid and reoxidation to the original spectrum with air.

A number of reductive acetylations of riboflavin have been carried out and the ultraviolet and infrared spectral of the product obtained, but so far the desired compound has not been obtained in crystalline form. The acetyl group on the ring is readily removed on a paper strip by development with dilute ammonia in butanol, the air then oxidizing the almost colorless substance to bright yellow, presumably riboflavin. A number of other reagents, including sodium hydroxide, were found not to produce this effect under comparable conditions.

N-Acetyl-S-butyrylmercaptoethylamine, 6,7-dimethylalloxazine, and 6,7,9-trimethylalloxazine have been prepared for enzymatic and chemical study.

Significance to Heart Research: This project is designed to help facilitate the studies on basic problems of intermediary metabolism carried out by various members of the Laboratory of Cellular Physiology.

Proposed Course of Research: Similar studies will be continued.

Analysis of NIH Program Activities

Budget Data Sheet

SERIAL NO. NHI-76

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 11,000	1	1	2	1	.33	1.33	--
FY 1956	\$ 11,000	1	1	2	1	.33	1.33	--

BUDGET ACTIVITY:

- RESEARCH
- ADMINISTRATION
- REVIEW & APPROVAL
- TECHNICAL ASSISTANCE

None

None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI-76

16. PUBLICATIONS:

A Resin for the Selective Retention of Sulfhydryl Compounds (with E. R. Stadtman and W. W. Kielley), J. Am. Chem. Soc. 76, 4041 (1954).

17. AWARDS AND HONORS: None.

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Cellular Physiology
and Metabolism

SERIAL NO.: NHI-77

PROJECT TITLE: 1. Enzymatic Degradation of Lysine, Serine and Glycine
2. The Role of C₁ Compounds in Intermediary Metabolism

PRINCIPAL INVESTIGATOR: Thressa C. Stadtman

OTHER INVESTIGATORS: None

PROJECT: 1. Enzymatic Degradation of Lysine, Serine and Glycine
2. The Role of C₁ Compounds in Intermediary Metabolism

Objectives: The objective of this research is to establish the biochemical pathways by which lysine, serine, glycine and one-carbon compounds are metabolized.

Methods Employed: Cell-free extracts are prepared of an anaerobic bacterium, Clostridium HF, which has been shown to have a particularly active amino acid metabolism. Studies on the dissimilation of lysine, serine and glycine by these cell-free preparations are carried out using the standard techniques of the enzyme chemists.

Major findings: Enzymes are present in extracts of Clostridium HF that catalyze the conversion of lysine to butyrate and acetate. The formation of acetate requires the presence of diphosphopyridine nucleotide, manganese and reduced lipoic acid. With certain enzyme preparations acetate and other unidentified neutral volatile compounds are produced from lysine. Identification of the latter compounds may throw light on the mechanism of butyrate synthesis from lysine. Glycine has been shown to undergo a reductive deamination to form acetate. A dithiol compound such as BAL and DPN are required for this enzymatic transformation. Preliminary tracer experiments show that the bacterial extracts catalyze the utilization of methanol for the biosynthesis of several non-volatile compounds the nature of which has not yet been determined.

Significance to Heart Research: This is one of the basic research projects of the Heart Institute established for the purpose of securing fundamental information on the intermediary metabolism of amino acids and one-carbon compounds. Basic information on these metabolic processes is essential to the ultimate understanding of heart metabolism as well as metabolism in general.

Proposed Course of Project: This project has been temporarily halted due to the absence of Dr. T. Stadtman, who is on a year's official leave of absence to study in the laboratory of D. D. Woods at Oxford, England, where she is continuing work on certain aspects of the above research program.

Analysis of NIH Program Activities
Budget Data Sheet

SERIAL NO.: NHI-77

BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 7,300	1	1	2	.33	.34	.67	--
FY 1956	\$ 9,400	1	1	2	1	1	2	--

BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

None

None

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

SERIAL NO.: NHI-77

PUBLICATIONS:

Discussion -- On the anaerobic degradation of lysine (in press).
McCollum-Pratt Symposium on Amino Acid Metabolism, June 14-17,
1954, Johns Hopkins University

On the Metabolism of an Amino Acid Fermenting Clostridium,
J. Bact. 67, 314 (1954)

Studies on the Microbiological Degradation of Cholesterol,
J. Biol. Chem. 206, 511 (1954)

Tracer Studies on Ornithine, Lysine, and Formate Metabolism
in an Amino Acid Fermenting Clostridium (with F. H. White, Jr.)
J. Bact. 67, 651.

HONORS AND AWARDS: Fellowship from the Helen Hay Whitney Foundation for
a year's study abroad with Dr. D. D. Woods at Oxford
University.

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute 2. LABORATORY: Cellular Physiology
and Metabolism

SERIAL NO.: NHI-78

PROJECT TITLE: Studies on the Structure of Bovine Pancreatic Ribonuclease

PRINCIPAL INVESTIGATOR: Robert R. Redfield

OTHER INVESTIGATORS: None.

PROJECT: Studies on the Structure of Bovine Pancreatic Ribonuclease

Objectives: The immediate objective of this research is to obtain basic information on the structure of proteins.

Methods employed: Proteolytic enzymes are allowed to partially digest DNP-oxidized ribonuclease. The polypeptide fragments thus obtained are isolated by chromatographic and "salting-in" procedures and are chemically degraded to determine the sequence of the various amino acids of which they are composed.

Major findings: Trypsin acting upon DNP-oxidized ribonuclease has been shown clearly to yield a digestion mixture of only four polypeptides, indicating an enzymatic splitting at only three sites in the molecule. One of these peptides possesses an N-terminal aspartic residue, and two possess N-terminal glutamic acid residues. By following the kinetics of the digestion in trypsin preparations which had been treated to preferentially inhibit contaminating chymotrypsin, as compared to untreated trypsin, it was concluded that the spurious end-groups previously obtained were attributable to the presence of trace amounts of contaminating chymotrypsin in the trypsin used. Also, conditions of digestion were established which yielded complete digestion by trypsin without appreciable hydrolysis from other sources. This makes available a rather simple mixture of large polypeptide subunits of ribonuclease with an average residue number of 32, which, when isolated, are sufficiently small to degrade by an experimental approach such as was used by Sanger.

A great deal of progress has been made in the separation and purification of these large polypeptides. Two of these have been purified to an extent that justified quantitative analysis of their constituent amino acid residues. The other two require further purification, but the necessary conditions for purification are now known in principle. The basic separation has been made possible by the "salting-in" principle as applied to the continuous dilution elution technique of Zahn and Stahl, the first time such an application has been made insofar as the investigator is aware.

Significance to Heart Research: This is one of the basic research projects of the Heart Institute aimed at the ultimate elucidation of the biochemical mechanism of protein biosynthesis and the mechanism of enzyme action. The present studies with ribonuclease are designed to obtain information about the fine structure of an enzyme molecule. This information is necessary for the development of any rational theory for the mechanism of substrate activation by enzymes or of specificity to enzyme substrate interaction. Such information

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Project Description Sheet Continued - NHI-78

will make available a more intelligent approach to the problem of protein biosynthesis in heart as well as in other tissues.

Proposed Course of Project: The next calendar year will be devoted to the degradation and determination of the amino acid sequence of the two peptides already purified, and the further purification and sequential analysis of the remaining two. It is expected that the coming year will see the conclusion of the amino acid sequence determination for the entire molecule. The location of the exact site of the disulfide bridges will then be undertaken.

Analysis of NIH Program Activities

Budget Data Sheet

SERIAL NO.: NHI-78

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$19,500	1	2	3	1	1.33	2.33	--
FY 1956	\$19,500	1	2	3	1	1.33	2.33	--

BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

None

None

R.P.C. 3
December 1954

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

SERIAL NO. NHI-78

PUBLICATIONS:

Studies on the Gross Structure, Cross-Linkages, and Terminal Sequences in Ribonuclease (with C. B. Anfinsen, W. L. Choate, J. Page, and W. R. Carroll), J. Biol. Chem. 207, 201 (1954)

HONORS AND AWARDS: None

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute 2. LABORATORY: Cellular Physiology
and Metabolism

SERIAL NO.: NHI-79

PROJECT TITLE: Enzymatic Degradation of the Cholesterol Side Chain

PRINCIPAL INVESTIGATOR: Marjorie G. Horning

OTHER INVESTIGATORS: None

PROJECT: Enzymatic Degradation of the Cholesterol Side Chain

Objectives: The immediate objective of this research is isolate and determine the chemical nature of unidentified co-factor(s) shown to be required for the oxidation of the side chain cholesterol to CO₂ by particulate enzyme systems obtained from liver.

Methods employed: The cofactor(s) present in the boiled extract of liver were purified by column and paper chromatography. The fractions eluted from paper were assayed in a mitochondrial system for activity. Although tedious, the methods are reproducible and should be applicable on a scale sufficiently large to permit isolation and identification of the cofactor(s).

Significance to Heart Research: Although cholesterol has been implicated as a causative agent in the etiology of atherosclerosis, its exact role is not known. It is possible that the deposition of cholesterol in the plaques is due to the inability of the body to dispose of this sterol through normal metabolic processes. The experiments described in this report should provide information about the cofactors required for cholesterol metabolism. After identification, these cofactors could be evaluated as dietary supplements in regulating cholesterol metabolism in humans.

Proposed Course of Research: The work will be centered on the isolation and identification of the cofactor or cofactors (in the boiled extract of liver) which are required for the degradation of the side chain of cholesterol. There are (at least) two other aspects of this problem which should be investigated. One of these involves the chemical structure of the products formed in this reaction, and this is now being studied by Dr. D. Fredrickson. The other is the isolation and characterizations of the enzymes present in washed mitochondria which are responsible for the degradation of cholesterol. It is expected that preliminary work will be done on this aspect of the problem.

Analysis of NIH Program Activities
Budget Data Sheet

Serial No. NHI-79

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 11,000	1	1	2	1	.33	1.33	--
FY 1956	11,000	1	1	2	1	.33	1.33	--

BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

None

None

Analysis of NIH Program Activities
Honors, Awards and Publications Sheet

SERIAL NO.: NHI-79

PUBLICATIONS:

The Synthesis of Radioactive L-Glutamic Acid, Richard W.
Hendler, Marjorie G. Horning and Christian B. Anfinsen,
Arch. Biochem. and Biophys. 51, 470 (1954)

HONORS AND AWARDS: None.

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-80
SERIAL NO.
6. Electrophoretic studies of serum proteins.
PROJECT TITLE
7. Robert S. Gordon, Jr.
PRINCIPAL INVESTIGATOR
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To put into full operation a new and highly accurate electrophoresis apparatus, and to analyze the protein composition of normal and pathological sera.

Methods Employed: The operation of the Aminco Model B electrophoresis apparatus.

Major Findings: Two major findings are already apparent, though a greater number of analyses is necessary to confirm them. The total protein concentration of normal human serum, expressed as gm. % dry weight, is higher than is usually believed, and the concentration of serum albumin tends to average 10% higher than published data indicate. The electrophoretic mobility of serum albumin is a closely defined physical constant, rather than the highly variable figure that one finds in the literature.

Significance to HEART Research: The electrophoretic method is of general usefulness in clinical pathology. Having it established in the Heart Institute makes it possible to analyze sera for protein disturbances in any of the clinical services. The results obtained to date are of real academic interest. This program is in line with the NHI policy of promoting vigorous basic research.

R. P. C. - 1
December 1954

9. PROJECT DESCRIPTION, Continued

Proposed Course of Project: In addition to making electrophoretic analysis available to other investigators where indicated, it is proposed to use this apparatus to study the interactions of unesterified fatty acids and other anions with serum proteins. These substances are evident by virtue of changes induced in the electrophoretic mobility of proteins with which they are combined.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-80
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 3,300	1	0	1	.50	0	.50	0
FY 1956	5,000	1	0	1	.50	0	.50	0

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Clinical Pathology Department, Biochemistry Service
Clinical Center, NIH

14. None known

.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHL-80
SERIAL NO.

6. None

7. None

Project Description Sheet

1. National Heart Institute 2. Cellular Physiology and Metabolism
INSTITUTE LABORATORY OR BRANCH

3. Metabolism 4. 5. NHI-81
SECTION SERIAL NO.

6. Study of the chemistry and physiology of unesterified fatty acids in plasma.
PROJECT TITLE

7. Robert S. Gordon, Jr.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the metabolic role of the small quantity of unesterified fatty acid present in all normal plasmas and to discover any alterations that may occur in disease states.

Methods Employed: The unesterified fatty acid content of plasma is determined by an electrometric titration after suitable extraction. In addition, radio-isotope-labelled fatty acids are employed in animal experiments.

Major Findings: The method for determining the fatty acid content of plasma has been exhaustively studied, modified where necessary, and found reliable. Analyses on a limited number of human subjects have revealed a uniform rise of the unesterified fatty acid level following a fatty meal, and a uniform fall following ingestion of glucose. Average normal fasting values have also been determined. The rate of turnover of an isotopically labelled fatty acid in the dog has been shown to be very rapid.

Significance to HEART Research: It is hoped that study of the mechanisms of fat transport will eventually reveal the etiology of atherosclerosis.

Proposed Course of Project: The studies that have been outlined will be amplified and confirmed. When the fasting levels of unesterified fatty acids, as well as the response to ingestion of fat and carbohydrate, have been thoroughly established in normals, various abnormal conditions will be investigated. Further isotope experiments in animals are planned in order to discover the metabolic fate of unesterified fatty acids.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-81
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 9,900	1	1	2	.50	1.00	1.50	0
FY 1956	11,600	1	1	2	.50	1.00	1.50	0

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13.

None

14.

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-81
SERIAL NO.

16. None

17. None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-82C
SERIAL NO.
6. Study of Clinical Nephritis and Nephrotic Syndrome
PROJECT TITLE
7. James H. Baxter and Howard C. Goodman
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: (1) To obtain more information regarding pathogenesis of the disease. (2) To study abnormalities in lipid and protein metabolism. (3) To study the effects of adrenal steroids in the disease, with particular attention at present to the new steroids, Metacortalone and Metacortin.

Methods Employed: Clinical studies on patients combined with laboratory studies on blood and urine.

<u>Patient Material (1954):</u>	<u>No.</u>	<u>Average Stay (Months)</u>
Admissions: Adult males	2	6
Adult females	1	4
Children males	3	4
Children females	3	2
Outpatients: No. of patients	20	
No. of visits	55	

Major Findings: Of 8 patients treated with steroids, 1(child) has been in complete remission for 8 months since therapy was discontinued, 2 (children) have been in complete remission for 6 months, but are on maintenance therapy, 2 (adult males) have improved gradually with

9. PROJECT DESCRIPTION, Continued

several courses of therapy, 1 (adult female) finally has had a good diuresis on discontinuing therapy but little change in proteins, 2 (children) are still on therapy with little change in the disease. The other patient apparently recovered from nephrosis with therapy for malaria which was present.

Significance to Heart Research: Nephritis and nephrotic syndrome fall into the large group of interrelated diseases known as cardio-vascular-renal diseases. The adrenal steroids often produce dramatic remissions in cases of the nephrotic syndrome. However, it is not clear how much is accomplished in terms of the long term results. One of the objects of the present study is to obtain more information regarding this point. The other clinical studies are directed toward a better understanding of the disease.

Proposed Course of Project: Our renal clinic will be continued, with admission of suitable patients for study and treatment.

1870

The first part of the document
 discusses the various aspects of
 the project and the progress made
 during the year. It also mentions
 the challenges faced and the
 solutions implemented. The second
 part of the document provides a
 detailed account of the financial
 status of the organization, including
 the income and expenditure for
 the year. The third part of the
 document discusses the future
 plans and the objectives for the
 coming year.

The document concludes with a
 statement of the Board of Directors
 and the members of the staff, who
 are committed to the success of
 the organization.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-82C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 6,600	2	2	4	.67	.33	1.00	820
FY 1956	9,000	2	2	4	.67	.33	1.00	1000

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (ITEM 1)

Drs. Orloff and Keitel of Lab. of Kidney and Electrolyte Metabolism have participated in this project. Also Dr. Pechet (GMETB) has participated, in the cases of patients treated with Metacortalone and Metacortin.

14. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-82C
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute 2. Cellular Physiology and Metabolism
INSTITUTE LABORATORY OR BRANCH

3. Metabolism 4. 5. NHI-83
SECTION SERIAL NO. :

6. Studies on Pathogenesis of Nephrotoxic Serum Nephritis
PROJECT TITLE

7. Howard C. Goodman and James H. Baxter
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the course and pathogenesis of nephrotoxic serum nephritis in rats and other animals, and the influence of drugs such as cortisone and heparin.

Methods Employed: Nephrotoxic serum is prepared by immunizing one animal with kidney tissue from another species. Animals injected with the serum are studied by means of chemical determinations of protein on urine and blood.

Major Findings: (1) Nephritis in rats due to rabbit anti-serum occurs immediately in most cases. Despite the fact that the disease persists during the life-time of the rat, we have been able to find no evidence of the autogenous production of nephrotoxic antibodies. (2) Cortisone and hydrocortisone do not affect the course of the disease. (3) Heparin produces a clearing of the lipemia with a decrease in plasma lipids almost to normal. Heparin may have some effect on proteinuria but the decrease is not consistent or dramatic.

Significance to Heart Research: Experimental nephritis in animals differs from the human disease in many respects but we believe that some of the basic mechanisms may be the same.

Proposed Course of Project: The disease produced in rabbits or rats by duck anti-kidney serum probably will be studied further because autogenous antibodies are said to be involved. The studies on effects of heparin will be continued, with the possibility of a therapeutic trial in patients in spite of the ineffectiveness in abolishing proteinuria in the experimental disease.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-83
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 6,600	2	2	4	.67	.33	1.00	
FY 1956	8,800	2	2	4	.67	.33	1.00	

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-83
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-84
SERIAL NO.
6. Study of the Mechanism of Proteinuria
PROJECT TITLE
7. Howard C. Goodman and James H. Baxter
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine whether proteinuria in experimental nephritis is due to increased passage of protein through the glomeruli, and/or to decreased tubular reabsorption of normally filtered protein.

Methods Employed: Two methods have been used to produce proteinuria in rats: (1) injections of nephrotoxic serum and (2) injections of small amounts of uranium. Plasma proteins of the rats with proteinuria and of normal rats have been labeled with Evans blue and the amount of blue dye present in the renal cortex determined after 24 hours.

Major Findings: The amount of blue dye employed was such that the amount of dye which appeared in the cortex of normal rats (as a result of reabsorption of filtered protein by the cells of the proximal convoluted tubule) was small. Under these circumstances, the renal cortices of rats which had received nephrotoxic serum contained large amounts of dye. This indicates that more protein than normal was being reabsorbed and therefore the proteinuria was a result of increased filtration. In case of the animals which had received uranium, the cortices contained less than normal dye indicating that the proteinuria produced by this procedure resulted (at least in part) from decreased reabsorption of normally filtered proteins (since glomeruli are unaffected histologically).

Significance to Heart Research: This study is directed toward a better understanding of the pathological physiology of renal disease.

Proposed Course of Project: It is planned later to investigate the metabolism of protein by renal tissue.

L.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

0. NHI-84
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 6,600	2	2	4	.33	.67	1.00	
FY 1956	8,200	2	2	4	.66	.67	1.33	

2. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

3. None

4. None known

L.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHI-84
SERIAL NO.

6. None

7. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-85
SERIAL NO.
6. Study on the Antigen in Nephrotoxic Serum Nephritis
PROJECT TITLE
7. James H. Baxter and Howard C. Goodman
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: (1) To determine the distribution in kidney and other tissues of the antigen capable of producing nephrotoxic serum.
(2) To prepare and characterize a soluble antigen derivative which will protect against nephrotoxic serum.

Methods Employed: Nephrotoxic serum is produced by repeated injections of rat kidney tissue into rabbits. Various tissues are studied for presence of antigen by (a) injecting tissues into rabbits and testing rabbit serum for ability to produce proteinuria in rats, and (b) testing ability of tissues to absorb antibodies and inactivate nephrotoxic serum. The soluble antigen derivative is prepared by digestion of kidney tissue by proteolytic enzymes. Following ultracentrifugation, the supernatant fluid is removed and subjected to dialysis, lyophilization and fractionation with ammonium sulfate.

Major Findings: (1) The antigen is present in renal cortex and medulla and is to some extent soluble in saline. Furthermore, it is present in lung in large amounts. (2) A soluble factor derived from the antigen has been prepared which is capable of neutralizing nephrotoxic antibodies in vitro or in vivo. This factor is destroyed by boiling but not by proteolytic enzymes. It is not (highly) antigenic. It apparently contains hexosamine, and is capable of producing the Schwartzman reaction.

Significance to Heart Research: Nephritis is one of the important causes of hypertension and cardiac disease. There is considerable evidence that nephritis in patients may be a result of the development of antibodies which attack the patient's own kidney tissue. Nephrotoxic serum nephritis in animals constitutes a model preparation for study which in some respects is thought to be analogous to the human disease.

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December 1954

PROJECT DESCRIPTION, Continued

Proposed Course of Project: The survey of tissues for antigen will be completed. We are interested to determine if antigen is present in skin and mucous membrane in addition to lung, since infections in these regions often are followed by nephritis. Efforts to purify and characterize the soluble protective factor will be continued. Ultimately an attempt may be made to obtain a similar preparation from human kidneys, looking toward possible therapeutic applications.

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December 1954

Analysis of NIH Program Activities

Budget Data Sheet

0. NHI-85
SERIAL NO.

1. BUDGET DATA:

	ESTIMATES EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 6,600	2	2	4	.33	.67	1.00	
FY 1956	8,500	2	2	4	.66	.67	1.33	

2. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

3. None

4. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-85
SERIAL NO.

16. PUBLICATIONS:

Neutralization of nephrotoxic sera by soluble material from
kidney digests, Proc. 5th Ann. Conf. on Nephrotic Syndrome, p. 105.

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE:

2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH

3. Metabolism
SECTION

4.

5. NHI-86
SERIAL NO.

- I. Immunochemical Studies of Lipoproteins
- II. Studies on the Chemical Composition of Chylomicrons
- III. Immunochemical Determination of Rate of Disappearance of Transfused Human Serum Albumin in a Patient with Idiopathic Hypoalbuminemia.

PROJECT TITLE

1. Elliott Middleton, Jr.
PRINCIPAL INVESTIGATOR

2. None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: I. To investigate the relationship between the protein moieties of the various classes of lipoproteins, specifically to test for the presence of protein common to Sf 3-8 beta-lipoprotein and chylomicrons.

II. To determine the chemical composition of plasma chylomicrons prepared in a standard manner.

III. To estimate the "half-life" of serum albumin in a patient with idiopathic hypoalbuminemia.

Methods Employed: I. Classical methods of immunochemistry have been used for analysis. Lipoprotein fractions have been prepared by flotation in the ultracentrifuge at appropriate solution densities.

II. Cholesterol phospholipid and neutral fat (by difference) were determined in Dr. J. Bragdon's laboratory by the methods in use there (please see Dr. Bragdon's report).

III. Human serum albumin was transfused into a patient with hypoalbuminemia and the albumin concentration in serum was followed at intervals using rabbit antiserum.

Major Findings: I.a. Experiments have been completed on the immunochemical relationship of Sf 3-8 beta-lipoprotein and chylomicrons. This work has shown the presence of protein(s) common to the high density of Sf 3-8 beta-lipoproteins and the very low density chylomicrons by (1) specific precipitation of antibody from anti-beta-lipoprotein rabbit sera by hydrolysed chylomicrons, (2) absorption of anti-beta-lipoprotein serum with chylomicrons removed antibody such that a second addition of chylomicrons produced much less specific precipitation, and (3) absorption of anti-beta-lipoprotein serum with beta-lipoprotein (Sf 3-8 removed part of the antibody capable of reacting with chylomicrons. (4) Hydrolysed chylomicrons do not react with anti-albumin serum.

I. b. The marked immunochemical inhomogeneity of ultracentrifugally and electrophoretically homogeneous Sf 3-8 beta-lipoprotein was confirmed and extended. Rabbit antisera to homogeneous (by physical criteria) beta-lipoprotein were studied by the quantitative precipitin reaction and agar gel diffusion analysis. The results indicated presence of at least 8 different antigen-antibody systems within the beta-lipoprotein-anti-beta-lipoprotein system.

I. c. Three alpha-lipoprotein preparations made in the ultracentrifuge have been examined for the presence of beta-lipoprotein and albumin by use of the corresponding antisera. In each preparation there was protein reactive with each of the antisera. Whether this represents actual contamination of ultracentrifugally prepared alpha-lipoprotein with beta-lipoprotein and albumin or whether it is an instance of true cross-reactivity has not been established.

II. The chemical composition of human plasma chylomicrons has been studied in conjunction with Dr. J. Bragdon. Chylomicrons were prepared by layering under saline the creamy material aspirated from the tops of hyperlipemic blood bank blood and centrifuging at 9500 G for 10 minutes. Only the packed buttery material was collected from the top of the centrifuge tubes. This material was resuspended in saline and the process repeated one or two times. Such washed chylomicron suspensions consisted largely of neutral fat with smaller amounts of cholesterol, cholesterol esters and phospholipid and with a small amount of protein, on the order of 1 percent or less by dry weight. The composition from one preparation to another was moderately variable and when different methods of preparation were employed the variability was marked. It appears that the lipid composition of the individual plasma and the method of preparation will determine the chemical nature of chylomicrons.

III. The data have been completed on the immunochemical estimation of rate of disappearance of transfused human serum albumin on the patient with idiopathic hypoalbuminemia. After normal albumin concentrations had been attained serum samples were analyzed at intervals for albumin by use of a calibrated rabbit antiserum against four-times recrystallized human serum albumin. A semilogarithmic plot of albumin concentrations against time permitted calculation of the "half-life" of the transfused albumin. The result was 38 days, an unusually long value.

Significance to HEART Research: I and II. Because of the demonstrated relationship between serum lipids and atherosclerosis an understanding of the metabolism and interrelationships of lipoproteins is of obvious significance in understanding vascular pathology.

III. Indirectly, information about serum albumin metabolism may help in understanding the genesis of edema and in certain forms of cardiac failure.

Proposed Course of Project: No further work will be done along the current lines of investigation since the writer is leaving the Public Health Service.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-86
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 6,600	1	0	1	1.00	0	1.00	
FY 1956	0	1	0	1	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

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December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHL-86
SERIAL NO.

6. PUBLICATIONS:

I. The Immunochemical Relationship of Human Plasma
Beta-Lipoprotein and Chylomicrons. (Submitted for publication to
Science)

7. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology & Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-87C
SERIAL NO.
6. Chemistry and Metabolism of Plasma Lipoproteins
PROJECT TITLE
7. Howard A. Eder
PRINCIPAL INVESTIGATOR
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: Lipids are transported in the plasma as constituents of complex proteins, the lipoproteins. While there is considerable knowledge about the lipid portion of these complex molecules almost nothing is known about the protein. It is important to know where, from what, and at what rate the lipoprotein protein (LPP) is synthesized. It is of importance to ascertain whether the lipoproteins participate equally in lipid transport or if the various lipoproteins have separate functions. Such studies might indicate how and where lipids are joined to proteins. They could answer the question as to whether interconversion of lipoproteins occurs both in normal fat metabolism and after heparin "clearing".

Methods Employed: Plasma lipoproteins have been tagged either in the lipid moiety by administration of $H_2P^{32}O_4$ or in the protein moiety by administration of C_7^{14} alanine. Thus far rabbits have been used as the experimental animal, although it is planned to study human subjects with N^{15} labeled glycine. Studies have been made of the rates of incorporation of these various substances with lipoproteins. Also labeled lipoproteins have been administered and their rates of decay and interconversion have also been measured.

Major Findings: The study on phospholipid transfer from lipoproteins has been concluded. It was found that rapid in vitro transfer of phospholipid from alpha to beta lipoprotein and vice versa occurred. Because of this fact it is evident that the metabolism of the individual lipoproteins cannot be studied by phospholipid labeling. Attention, therefore, has been directed toward the study of the protein portion of the molecule.

(Major Findings, Continued)

Preliminary studies carried out with Dr. Daniel Steinberg have indicated that the LPP of rabbits can be satisfactorily labeled by the administration of C^{14} in the carboxyl carbon. In our first such experiment the specific activity of the beta LPP rose rapidly and was maximal after 6 hours. The specific activity rapidly fell by 24 hours and then declined gradually thereafter. Both the alpha LPP and the remaining serum proteins did not attain the high activity of the beta LPP. They reached their maximal specific activities at 24 hours and their activity then declined. Interpretation of these data awaits further experimentation.

An experiment is currently in progress in which a rabbit was injected with a large quantity of labeled alanine and then exsanguinated after 6 hours. The lipoproteins were separated and each component has been injected into recipient rabbits. The activity is being determined in each fraction of the recipient rabbits serially. This experiment should provide further information about the dynamics of the LPP turnover and should also tell us whether interconversion of lipoproteins occurs.

Significance to Heart Research: Since it has been demonstrated that the occurrence of atherosclerosis is related to the presence of certain lipoproteins in the plasma it is obvious that studies of the metabolism of these substances are necessary for the understanding of their role in disease.

Proposed Course of Project: The studies outlined above will be continued. Turnover studies by 2 techniques are to be carried out in larger animals. N^{15} labeled glycine is being synthesized for administration to normal man. The turnover of the lipoproteins will be determined and compared with the turnover of other isolated plasma proteins. Similar studies will be carried out in a dog using C^{14} labeled alanine.

The in vitro studies with heparin clearing described in the previous report will also be carried out. These results will be of special interest in light of Dr. Edward Korn's observation that triglycerides must combine with alpha lipoprotein before they can react with lipoprotein lipase.

Patient material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay</u> <u>Days</u>
Admissions: Adult males	3	14
Adult females	2	7
Outpatient: Number of patients	2	
Number of visits	4	

R.P.C. - 2
December 1954

Analysis of NIH Program Activities
Budget Data Sheet

10. NHI-87C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 11,600	1	1	2	1	1	2	
FY 1956	11,600	1	2	3	1	1.33	2.33	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHI-87C
SERIAL NO.

6. PUBLICATIONS:

- I. Atherosclerosis and aortic stenosis in hypercholesterolemic xanthomatosis. Barr, D.P., Rothbard, S., and Eder, H.A. Jour. Amer. Med. Assn. 156, 943, 1954.
2. Protein-lipid relationships in human plasma.
- III. In pregnancy and the newborn. Russ, E.M., Eder, H.A., and Barr, D.P. J. Clin. Invest. 33, 1662, 1954.
- IV. The in vitro exchange of phospholipid phosphorus between lipoproteins. Eder, H.A., Bragdon, J., Boyle, E., Circulation 10, 603, 1954.

7. HONORS AND AWARDS:

1. Received travel grant from International Association of Gerontology to attend International Congress in London, July, 1954.
2. Appointed Associate Professor of Medicine, N. Y. State Univ. College of Medicine at N. Y. City, effective March 1, 1955.

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-88C
SERIAL NO.
6. Physical, Chemical, Biological Studies of Lipoprotein Transport and
PROJECT TITLE Metabolism and its Relationship to Atherosclerosis.
7. Edwin Boyle
PRINCIPAL INVESTIGATOR
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To describe the abnormal lipid patterns occurring in various disease states, to determine the nature of the metabolic abnormality leading to these altered lipid patterns and to explore therapeutic patients potentially of value in these conditions.

Methods Employed: Ultracentrifugal analysis of serum lipoproteins by the methods devised by Gofman and co-workers. Electrophoretic and chemical analysis for correlation with ultracentrifugal results.

Administration of heparin and/or estrogenic compounds to patients with xanthoma tendinosum, xanthoma tuberosum, biliary cirrhosis and other disease states associated with hyperlipemia.

Major Findings: Effects on the vascular status as well as skin lesions of xanthoma patients concomitant to alterations in their serum lipids have been studied. We have established that "normalizing" serum lipid transport in xanthoma tuberosum patients has resulted in disappearance of skin lesions and improvement in vascular disease in two patients. This has been accomplished with both heparin and estrogen. These therapeutics have been ineffective in altering the clinical picture of two cases of biliary cirrhosis.

Significance to Heart Research: The correlation between abnormal serum lipoproteins and the development of atherosclerosis is a fairly well established one. If a therapeutic agent could be found that would maintain serum lipoproteins in the normal state over prolonged periods of time it would be possible to evaluate this correlation experimentally in the sense that the course of the arterial lesions might be altered.

9. PROJECT DESCRIPTION, Continued

The study of disordered lipoprotein metabolism in general may lead to an understanding of the particular abnormalities found in patients with arterosclerotic heart disease.

Proposed Course of Project: A continuation of the present researches which will also include thyroid administration and β -sitosterol administration appears profitable. Chemical studies on individual lipoprotein components in both normals and hypercholesterolemic patients will be continued.

<u>Patient Material:</u> (1954 calendar year)		No.	Average Stay <u>Days</u>
Admissions:	Adult males	15	22
	Adult females	12	58
Outpatient:	Number of patients	19	
	Number of visits	200	

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-88C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$19,900	1	2	3	1	2	3	1825
FY 1956	12,000	1	2	3	1	2	3	1000

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (ITEM 1)

Part of these studies have been done in collaboration with Dr. Charles F. Wilkinson, Jr., at New York University Post-Graduate Medical School, Bellevue Hospital, New York City.

14. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-88C
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR
1954:

Production of Lipemia Clearing Factor During Anaphylactoid Shock.
Havel, R., and Boyle, E., Proc. Soc. Exp. Bio. and Med. 85, 468-472, 1954.

The Effect of Varying the Intake of Sitosterol on the Lipid Fractions
of Human Serum. Wilkinson, Jr., C.F., Boyle, E., Jackson, R.S., Benjamin,
M.R. In Press.

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-89-C
SERIAL NO.
6. Studies on the Metabolism of Fructose
PROJECT TITLE
7. Daniel Steinberg and Martha Vaughan
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION:

Objectives: To determine to what extent the substitution of fructose for glucose in the diet might fulfill the carbohydrate requirement of a diabetic animal since it is known that fructose feeding can repair some of the metabolic derangements in diabetes.

Methods Employed: Diet studies in alloxan diabetic rats. An attempt to prevent the development of diabetic ketosis in one patient by means of fructose administration.

Major Findings: It appears that in diabetic rats the beneficial effect of fructose, if any, is very small. Ketosis could not be prevented by fructose in a diabetic patient deprived of insulin.

Significance to Heart Research: It is known that there are certain disturbances of fatty acid and cholesterol metabolism in diabetes which may be related to the development of atherosclerosis in this disease. Further information concerning these problems may be of help in the understanding of both diabetes and atherosclerosis.

Proposed Course of Research: It is planned to determine by direct measurements using C¹⁴-labelled fructose the amount of this sugar which can be utilized as compared with glucose in normal and diabetic rats.

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December 1954

(NHI-89-C)

9. PROJECT DESCRIPTION, Continued

Patient material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult male	1	70
Outpatient: Number of patients	1	
Number of visits	6	

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-89-C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$13,300	2	4	6	.67	1.33	2.00	70
FY 1956	15,300	2	4	6	.67	1.33	2.00	150

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-89-C
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHL-90
SERIAL NO.
6. The Inactivation of Insulin by an Enzyme from Rat Liver
PROJECT TITLE
7. Dr. Martha Vaughan
PRINCIPAL INVESTIGATOR
8. None
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To isolate and purify insulinase in order to study the reactions by which insulin is inactivated and degraded and to determine the nature of the end products.

Methods Employed: Fractionation of liver extracts, and assay of insulinase activity by inactivation of and non-protein nitrogen formation from insulin. Identification of peptides formed from insulin by paper chromatography and other techniques.

Major Findings: The enzyme has now been purified about 40-fold from rat liver. Insulin inactivation and proteolytic degradation of insulin by the enzyme are parallel in all experiments thus far. The enzyme hydrolyzes oxidized insulin and is inhibited by diisopropylfluorophosphate. It is not destroyed by ribonuclease.

Significance to Heart Research: Through some undefined action insulin has a marked effect on cholesterol and fatty acid metabolism. Since metabolism of these substances seems to be related to the development of atherosclerosis, knowledge of the metabolism and action of insulin may contribute to a better understanding of these processes.

Proposed Course of Research: Work on the isolation and purification of insulinase from beef liver. Identification of the breakdown products of insulin in this reaction. Study of the effects both in vivo and in vitro of a drug which has been reported to be an inhibitor of insulinase.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-90
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$11,600	1	4	5	.33	1.67	2.00	
FY 1956	13,600	1	4	5	.33	1.67	2.00	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-90
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Inactivation of Insulin by an Enzyme from Rat Liver,
M. Vaughan, Biochim. et Biophys. Acta 15, 432 (1954)

Non-Uniform Labeling of Insulin and Ribonuclease Synthesized
in Vitro, M. Vaughan and C. B. Anfinsen, J. Biol. Chem. 211, 367 (1954)

17. None



Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHL-91-C
SERIAL NO.
6. (1) Enzymatic Degradation of Cholesterol (2) Metabolism of Physiological
PROJECT TITLE Fat Emulsions (Chylomicrons)
7. Donald S. Fredrickson (also clinical resident during this period)
PRINCIPAL INVESTIGATOR
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: 1. Investigation of the enzymatic metabolism of cholesterol.
2. A study of the metabolism of radioactive lipoproteins by whole animals and isolated tissues.

Methods Employed: Radioactive cholesterol is incubated with cell-free preparations from liver under suitable conditions and the products of metabolism are recovered and characterized. Chylomicron lipoproteins tagged with radioactive carbon are isolated from lymph; their fate in animals or isolated tissue preparations, and behavior with respect to other lipoprotein classes is studied. The methods utilized for isolation and identification include solvent partition, paper and column chromatography, differential precipitations, radioactive assay, and spectrographic analysis.

Major Findings: Available methods for identification of steroids by paper chromatography have been improved. Two products of cholesterol metabolism other than carbon dioxide have been isolated, one identified as an ester, and a second more polar than cholesterol partially identified. Lipids in chylomicrons have been shown to exchange little or not at all with other serum lipoproteins of greater density.

Significance to Heart Research: A basic understanding of the transport and cellular metabolism of fats is essential to clarification of the role of lipids in atherosclerosis and for a rational approach to therapy.

Proposed Course of Research: The identification of the cholesterol degradation products will be completed. Attention will be given to studies of lipoprotein transfer in vivo, and the metabolism of chylomicron lipids by tissues, with emphasis upon adipose tissue. Extension of the studies to human subjects using stable isotopes is planned.

Patient Material: None for calendar year 1954.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-91-C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 6,600	1	0	1	1	0	1	0
FY 1956	10,000	1	0	1	1.34	0	1.34	70

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE
IN P.H.S., IDENTIFY SUCH RESEARCH:

Complements similar studies being conducted by Dr. M. Horning, Cellular
Physiology Lab., NHI.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-91-C
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-92
SERIAL NO.
6. O^{18} exchange with dicarboxylic amino acids and their amides.
PROJECT TITLE
7. Daniel Steinberg and Simon Rothberg
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To investigate the mechanism of enzymatic and non-enzymatic dicarboxylation of aspartic and glutamic acids. To find conditions for hydrolysis of glutamine and asparagine that lead to the exchange of only one oxygen atom. The latter part of the problem is directed ultimately at devising a method for measuring the content of these amides in proteins.

Methods Employed: After alkaline or acid hydrolysis under varying conditions in the presence of H_2O^{18} the percentage exchange of oxygen atoms is determined. An acetone powder of *Cl. Welchii* is used for the enzymatic dicarboxylations. Conventional methods for O^{18} analysis in the mass spectrometer are used.

Major Findings: Preliminary results indicate that alkaline hydrolysis does not lead to oxygen exchange with dicarboxylic amino acids whereas acid hydrolysis leads to rapid exchange. Methods for purification of aspartic acid have been developed and a chromatographic method for isolating asparagine has been set up.

The enzymatic dicarboxylation does involve exchange of oxygen with water but results have been too variable to permit final statements to be made.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet
CONTINUED

(NHL-92)

Significance to Heart Research: This project is a part of the basic research program of the NHI. While it does not relate specifically to heart disease the knowledge gained relative to cellular metabolism in general will contribute to furthering our understanding specifically of cardiovascular function.

Proposed Course of Project: The next two months will be devoted to establishing reliable figures for the exchange during enzymatic dicarboxylation, then an intensive effort to perfect the methods involved in determining asparagine and glutamine will be made.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-92
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 8,300	2	0	2	.33	1.00	1.33	
FY 1956	10,500	2	0	2	.33	1.00	1.33	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-92
SERIAL NO.

16. None

17. None

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P.C. - 1
ember 1954

Analysis of NIH Program Activities

Project Description Sheet

National Heart Institute
INSTITUTE

2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH

Metabolism
SECTION

4.

5. NHI-93C
SERIAL NO.

Assay of serum transaminase as a diagnostic aid in coronary artery disease
PROJECT TITLE

Daniel Steinberg
PRINCIPAL INVESTIGATOR

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To perfect the enzymatic assay and to evaluate it as a diagnostic tool.

Methods Employed: Glutamic-oxalacetic transaminase is assayed by a modification of the method of LaDue. The reaction is coupled with malic dehydrogenase and the rate of disappearance of DPNH is determined. Patient material for this study is supplied by the Cardiac Service at George Washington University Hospital and Dr. Bernard Ostrow of that hospital is collaborating on this project.

Major Findings: Two significant modifications of the original method were necessary: (1) The preincubation period should be at least 1/2 hour instead of 10 minutes. (2) The rate of the reaction during the 1 or 2 minutes after addition of substrate is submaximal so that the rate after the third minute should be used in calculating enzyme concentration.

Over 30 cases have been studied to date and in at least 90% of the cases diagnosed clinically and by electrocardiogram as myocardial infarction the transaminase has also been positive. In some instances the clinical diagnosis was obscure while the transaminase test was clearly positive.

Elevations have been found in patients with chronic liver disease and in patients recently subjected to surgery.

Significance to HEART Research: The importance of establishing or ruling out the diagnosis of myocardial infarction is clear. Even with the electrocardiogram there is not infrequently an unresolvable doubt as to whether infarction has occurred or whether the patient has pain due to coronary insufficiency without infarction. The results obtained so far suggest that this new diagnostic criterion may be of real value to the cardiologist.

Proposed Course of Project: Collaboration with Dr. Ostrow will continue until a series of 50 cases has been collected. At that time it is hoped that George Washington University Hospital will be able to set up the enzymatic assay and the project will be discontinued here.

Patient material: (1954 calendar year)

No patients were admitted to the Clinical Center specifically for this project. However, blood samples have been studied from about 15 Clinical Center patients admitted and being studied in other projects.

P.C. - 2
ember 1954

Analysis of NIH Program Activities

Budget Data Sheet

NHI-93C
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 5,000	1	1	2	.34	.33	.67	
FY 1956	0	0	0	0	0	0	0	

BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1

George Washington University Hospital - Dr. Ostrow.

Nones known

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[Faint, illegible text block]

[Faint, illegible text block]

P.C. - 3
ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHL-93C
SERIAL NO.

None

None

Analysis of NIH Program Activities

Program Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
SECTION
- 4.
5. NHI-94
SERIAL NO.
6. Studies on the Mechanisms of Protein Synthesis and Degradation in normal
PROJECT TITLE tissues.
7. Daniel Steinberg and Martha Vaughan
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS

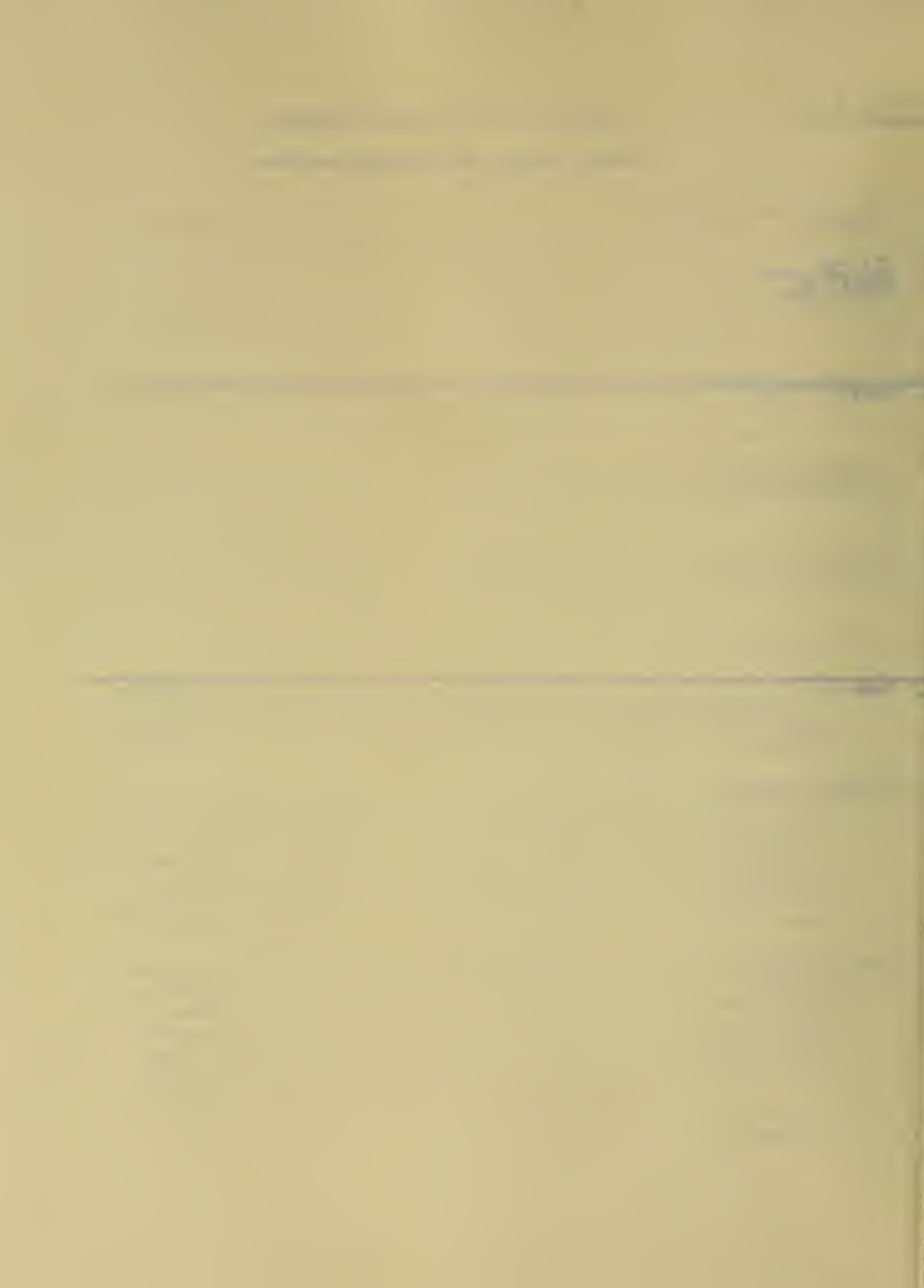
9. PROJECT DESCRIPTION

Objectives: To elucidate the mechanism by which amino acids are assembled in the proper sequence to form specific proteins. To determine the nature of the "proteolytic" processes which are implied as a constant concomitant of synthesis in the dynamic state.

Methods Employed: C^{14} -labeled amino acids are incubated in vitro with tissue slices or homogenates under various conditions and the pattern of uptake into specific proteins or the total tissue protein is determined. Protein degradation in vitro under physiological conditions is followed either by measurements of non-protein nitrogen or by measurement of the release of C^{14} amino acids from tissues previously tagged by injection of labeled amino acids into the whole animal.

Major Findings: The normal pattern of protein degradation in liver slices and kidney slices has been determined. It has been demonstrated that this process is inhibited by 2,4 - dinitrophenol. An unexpected finding is that amino acid analogues at concentrations that inhibit protein synthesis also inhibit protein degradation. This may imply that synthesis and degradation have at least some steps in common.

It has been shown that no appreciable amount of the amino acid incorporation in vitro occurs by transpeptidation or other non-energy requiring process.



Analysis of NIH Program Activities

Program Description Sheet

National Heart Institute
INSTITUTE

2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH

Metabolism
SECTION

4.

5. NHI-94
SERIAL NO.

Studies on the Mechanisms of Protein Synthesis and Degradation in normal
PROJECT TITLE tissues.

Daniel Steinberg and Martha Vaughan
PRINCIPAL INVESTIGATORS

None
OTHER INVESTIGATORS

PROJECT DESCRIPTION

Objectives: To elucidate the mechanism by which amino acids are assembled in the proper sequence to form specific proteins. To determine the nature of the "proteolytic" processes which are implied as a constant concomitant of synthesis in the dynamic state.

Methods Employed: C^{14} -labeled amino acids are incubated in vitro with tissue slices or homogenates under various conditions and the pattern of uptake into specific proteins or the total tissue protein is determined. Protein degradation in vitro under physiological conditions is followed either by measurements of non-protein nitrogen or by measurement of the release of C^{14} amino acids from tissues previously tagged by injection of labeled amino acids into the whole animal.

Major Findings: The normal pattern of protein degradation in liver slices and kidney slices has been determined. It has been demonstrated that this process is inhibited by 2,4 - dinitrophenol. An unexpected finding is that amino acid analogues at concentrations that inhibit protein synthesis also inhibit protein degradation. This may imply that synthesis and degradation have at least some steps in common.

It has been shown that no appreciable amount of the amino acid incorporation in vitro occurs by transpeptidation or other non-energy requiring process.

R.P.C. - 1
December 1954

(NHI-94)
(SERIAL NO.)

9. PROJECT DESCRIPTION, Continued

In contrast to results reported using tumor cells we have found that it is not possible to overcome the inhibition of valine incorporation by o-fluorophenylalanine even with valine concentrations up to 5×10^{-3} M.

Significance to Heart Research: This project is a part of the basic research program of the National Heart Institute. While it does not relate specifically to heart disease the knowledge gained relative to cellular metabolism in general will contribute to furthering our understanding specifically of cardiovascular function.

Proposed Course of Project: The findings in slice systems are to be checked in homogenates. It is hoped that intermediate products in the degradative metabolism of proteins can be identified, particularly when the process is inhibited by amino acid analogues. Labeled o-fluorophenylalanine would make it possible to determine the fate of the analogue more readily and synthesis of this compound is planned.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-94
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 19,800	2	4	6	.33	2.67	3.00	
FY 1956	23,000	2	4	6	.66	2.67	3.33	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHL-94
SERIAL NO.

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Steinberg, D., A New Plakalbumin-like Protein. Comptes rendus des Travaux du Laboratoire Carlsberg, Ser.Chim. 29, No. 10 (1954)

Steinberg, D., Some Observations on the Initial Reaction in Plakalbumin Formation. Comptes rendus des Travaux du Laboratoire Carlsberg, Ser. Chim. 29, No. 11 (1954)

7. None

Analysis of NIH Program Activities

Program Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
3. Metabolism
SECTION
- 4.
5. NHI-95-C
SERIAL NO.
6. Serum Lipoproteins
PROJECT TITLE
7. Joseph H. Bragdon, Richard J. Havel
PRINCIPAL INVESTIGATORS
8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study serum lipoproteins, their character, interconversions, fate, and relation to atherosclerosis.

Methods Employed: Various lipoprotein classes are separated by differential ultracentrifugation. The chemical composition of the classes is then determined. In some cases isotopically labeled lipoproteins are used.

Major Findings: Improvements in methods for quantitative recovery and analysis of serum lipoproteins.

Separated lipoprotein classes have been injected into rats. When alpha lipoproteins or Sf 2-8 are injected, then Sf 20-80 appear in the recipient's serum. The effect is similar to that observed following Protamine injection.

Several inorganic salts, including phosphotungstate, phosphomolybdate, silicotungstate, and sodium polymetaphosphate, have been shown to resemble heparin in anticoagulant effect and in ability to release clearing factor into the blood stream.

Observations on hyperlipemia and atheromatosis in the ground squirrel have been completed. This species is a hibernator. It appears that in periods of caloric excess lipids accumulate in the blood faster than they can be removed by the depots.

The presence of a cholesterol-free lipoprotein, suspected by Turner, has been confirmed. It accounts for about 10% of the serum phospholipid instead of the 60% surmised by Turner.

THE UNIVERSITY OF CHICAGO

PHILOSOPHY DEPARTMENT

PHILOSOPHY 101

LECTURE NOTES

LECTURE 1

THE PHENOMENON OF CONSCIOUSNESS

1.1 THE HARD PROBLEM

1.2 THE SOFT PROBLEM

1.3 THE MEASUREMENT PROBLEM

1.4 THE INFORMATION PROBLEM

1.5 THE COMPLEXITY PROBLEM

1.6 THE INTEGRATION PROBLEM

1.7 THE REDUCTION PROBLEM

9. PROJECT DESCRIPTION, Continued

Patient material: (1954 calendar year)

	<u>No.</u>	<u>Average Stay Days</u>
Admissions: Adult males	3	50
Adult females	2	56
Outpatient: Number of patients	0	

Significance to Heart Research: Evidence is accumulating that a major factor in the pathogenesis of atherosclerosis may be the concentration and/or composition of certain lipoprotein classes in the serum. It therefore becomes important to develop accurate methods for quantitating and characterizing them. With proper tools knowledge can be gained of the factors which control their metabolism and their functions in health and disease.

Proposed Course of Project: Efforts will continue toward improvement of techniques, particularly those utilizing isotopes. Studies will be made on the role of lipoproteins in fat metabolism and transport.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-95-C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$ 23,200	2	2	4	2	2	4	90
FY 1956	23,600	2	2	4	2	2	4	0

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None

14. None known

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-95-C
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Production of lipemia clearing factor during anaphylactoid shock.
Havel, R., and Boyle, E. Proc. Soc. Exp. Biol. 85, 468, 1954

In vivo effect of anti-heparin agents on serum lipids and lipoproteins. Bragdon and Havel: Am. J. Physiol. 177, 128, 1954.

Hyperlipemia and atheromatosis in a hibernator: Citellus Columbianus.
Bragdon, J. Circ. Res. 2, 520, 1954.

17. None

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Small handwritten text or signature in the upper right corner.

Main body of handwritten text, consisting of several lines of cursive script.

Handwritten text at the bottom of the page, possibly a footer or concluding remarks.

R.P.C. - 1.
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Cellular Physiology and Metabolism
LABORATORY OR BRANCH
3. Metabolism
Section
5. NHI 96C
SERIAL NO.
6. Study of the Underlying Factors Associated with Atherosclerosis
PROJECT TITLE
7. Four positions requested for FY 1956
PRINCIPAL INVESTIGATOR(S)
8. Five positions requested for FY 1956
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION:

It is anticipated that additional funds requested for F.Y. 1956 will be used for intensified studies of the large fat-bearing proteins in circulating blood, and of the synthesis and liberation of heparin.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-96C

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	0	0	0	0	0	0	0	--
FY 1956	\$48,000	4	5	9	4	5	9	500

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

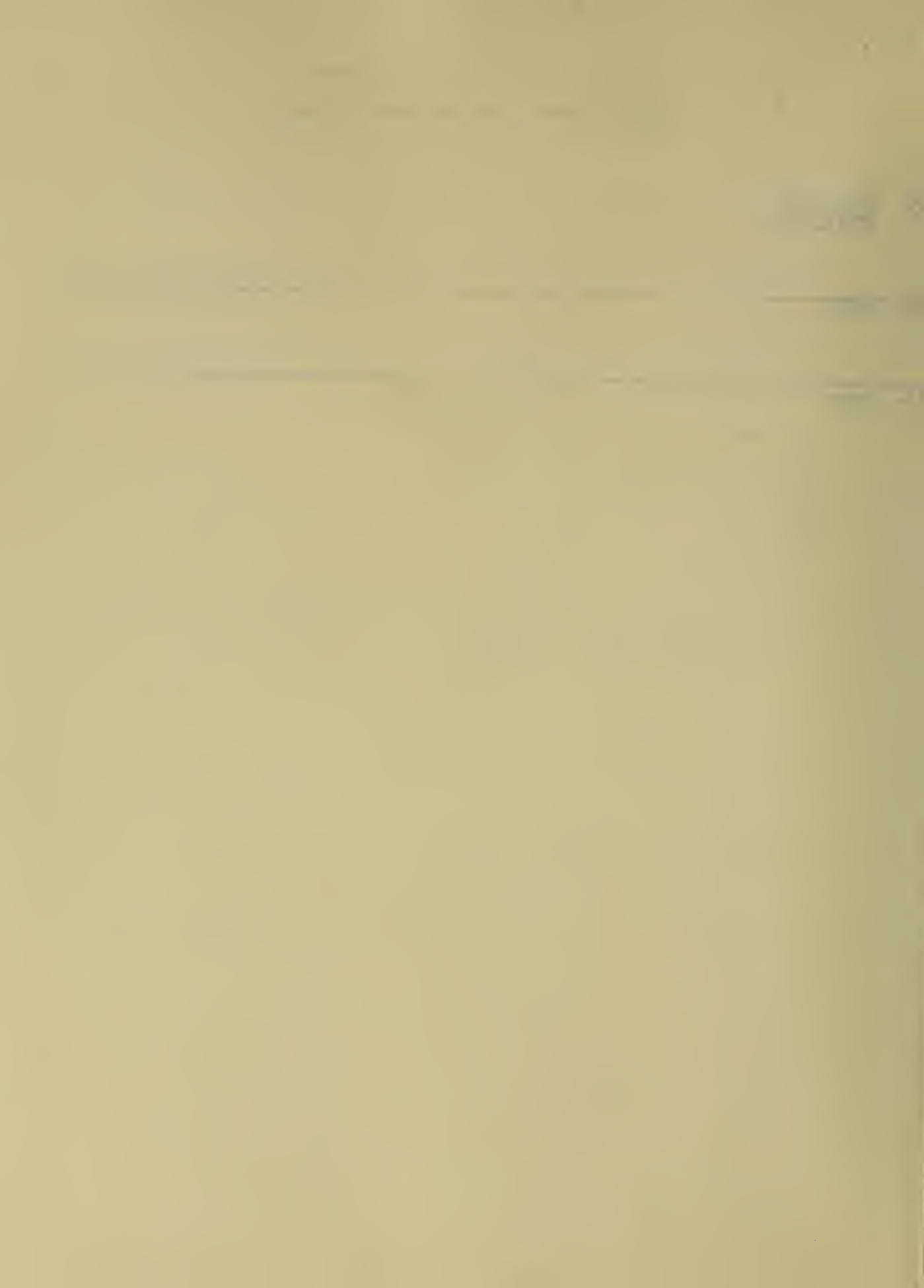
14. None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 96C
SERIAL NO.

16. None

17. None



Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE

2. Gerontology
LABORATORY OR BRANCH

4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)

5. NHI-97C
SERIAL NO.

6. Cardiovascular Hemodynamics. I. Arterial Performance in Man.
PROJECT TITLE

7. Hilton Landowne (1/3 time)
PRINCIPAL INVESTIGATOR (S)

8. C.O. = G. W. Gaffney (1/2 time)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To investigate the functioning of the arterial circulation in living human subjects in the following manner:

- a. To develop and to test critically methods of studying the dynamic behavior of large and medium sized arteries in site.
- b. Using these, and existing methods, to describe individual, and age-wise differences in arterial function in ostensibly normal subjects of mature age.
- c. To characterize evidences of pathophysiological performance in arteriosclerosis, hypertension and other circulatory disorders.

Methods employed: The way in which arteries function to transmit pressure and flow from the heart to the small blood vessels is determined by arterial elastic and viscous properties. We have been studying pressure transmission by two methods: a. Small transient, or sustained waves are induced in arteries by a method developed in this laboratory. b. The pressure pulse produced by the heart is subjected to harmonic analysis.

Pertinent interarterial pressures are detected at various positions within the arterial tree by intra-arterial needles and special catheters attached to capacitance type sensing devices, and recorded, with sensitive and accurate equipment.

The speed of pressure propagation, and its distortions, damping, resonance and reflection are then computed at varying pressures, and for waves of different frequencies. These data provide indices of elastic and viscous behavior.

Clinical material: Subjects are obtained from our 60 bed male ward, and from other wards of the hospitals.

Major findings: The distensibility of a living artery varies considerably with the arterial pressure, and also with the rate at which pressure is changing. Rapid changes of pressure effect less stretch of the arterial wall than do equal, more gradual changes. This is also true in hypertensive disorders.

Substantial agreement has been obtained between both methods of study used, for the arteries of the arm, where both can be compared.

Most of the pressure energy of the pulse is contributed by waves of relatively low frequency. These are readily reflected, and persist in the artery, while higher frequency waves are readily damped. The presence of reflected waves complicates the analysis.

The conventional physiological method of measuring pulse wave propagation fails to provide this information. Arteries cannot satisfactorily be considered to conform to ideal elastic tubes but are more adequately described in terms of the rheology of long chain polymers which make up living fibers.

Significance to heart research: Represents advance in concepts and in knowledge of the physiology of the circulation in human subjects.

Illustrates the role of more basic scientific inquiry in human circulatory physiology.

Proposed course of project: Central pressure analyses are to be studied in subjects of varying age, and in hypertensive disease.

Separation of the influence of reflected components will enable us to obtain parameters of wave propagation determining operative distensibility in central arteries.

Studies will be prepared for publication.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-97C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	11,600	2	1	3	.83	1.00	1.83
FY 1956	11,600	2	1	3	.83	1.00	1.83

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals

14. None.

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-97C
SERIAL NO.

16. None.

17. None.

December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHL-98C
SERIAL NO.

6. Hemodynamics. II. Cardiac Performance in Man.
PROJECT TITLE

7. Milton Landowne (1/3 time)
PRINCIPAL INVESTIGATOR(S)

8. C.O. J. A. Falzone (1/3 time)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study the performance and functional limitations of the living human heart as affected by age and disorders of the circulation.

Methods employed: Studies in sizeable number of normal subjects require techniques which are generally acceptable to the subjects. Cardiac output was measured in duplicate by a dye dilution technique, and brachial intra-arterial pressure was measured by needle puncture and resistance strain gage.

Clinical material: Sixty-seven subjects from our ward and the general hospital, free of discernible clinical evidence of cardiovascular disorder.

Major findings:

- (1) A significant agewise decline in cardiac output was observed. This is due to a decrease in stroke index, augmented by decreases in heart rate and body size.
- (2) The average rate of decline in the circulation and increase in resistance exceeds the reported rates of reduction in basal metabolism and in estimated total, or active cell mass. Therefore, in general, circulatory attrition with age is more likely to be primary to the decline in total cellular activity.
- (3) The increase in total vascular resistance with age is proportionately greater in some circulatory segments than in others.
- (4) The estimated resting cardiac work declined with age because the decrease in output more than balances the change in blood pressure.
- (5) Despite a reduction in work there is a reduction in heart rate and a prolongation of systolic duration; so that estimates of "power", or the rate of work show an agewise decline. These are evidences of altered cardiac performance.
- (6) The increase in a subjective circulation time with age, is paralleled by an increase in objective dye circulation time, and reflects a decreased mean velocity of blood flow.
- (7) Estimates of central arterial elasticity are highly age correlated, but show individual variability which does not allow reliable predictions of cardiac output to be made from blood pressure and age.

Significance to heart research: Represents a contribution to the understanding of the function of the heart and the total circulation, and how these are affected by age.

Provides reliable normative information about cardiovascular function in man, and its age trends, for clinical as well as research use.

Enables improved clinical identification of disorders of the heart and aorta.

Proposed course of project: We plan to study similar measures of cardiac performance during exercise. We shall try to determine whether a limitation of total cardiac output limits the function of other organs, i.e. lungs, voluntary musculature.

Estimates of central arterial elasticity can be improved. This may permit the determination of cardiac performance from blood pressure records.

Interest in age changes in the ballistocardiogram has prompted a study of the role of extra-cardiac factors concerned with force transmission by the body.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-98C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURE	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	15,000	2	2	4	.67	2.00	2.67
FY 1956	15,000	2	2	4	.67	2.00	2.67

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-98C
SERIAL NO.

16. None.

17. None.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-99C
SERIAL NO.
6. Cardiovascular Hemodynamics. III. The Peripheral Circulation in Man.
PROJECT TITLE
7. Milton Landowne (1/3 time)
PRINCIPAL INVESTIGATOR(S)
8. C.O. G. W. Gaffney (1/2 time)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study the circulation in the extremities of living human subjects, with respect to changes with age, disorders in function, and to increase our understanding of factors governing the blood flow to these tissues.

Methods employed: In a controlled environment, the skin temperature and the response of skin temperature to a standardized vasodilator stimulus, have been employed as useful secondary indices of thermal exchange and of the circulation to the skin.

Clinical material: One hundred and nine male subjects in whom a careful clinical evaluation of the peripheral circulation has been made. These are from our ward, the staff and the general hospital. Studies are acute.

Major findings: In subjects clinically free of peripheral vascular disease, toe temperature increased with age while finger temperature did not change. In older subjects toes were warmer than fingers. This suggests that there is an age change in the manner of heat dissipation by the extremities. It indicates no diminution in resting circulation with age.

Normal standards have been obtained for resting temperature and the response to a vasodilating stimulus.

Among some subjects above the sixth decade without clinical evidences of disordered circulation, the response to a vasodilating stimulus was similar to that of some patients with manifest peripheral vascular disease. Other older subjects had good response, indicating our ability to detect functional impairment in subjects without symptoms or other signs of clinical disorder.

Significance to heart research: Describes the peripheral vascular responses of "normal" adult and older men, providing standards.

Shows how commonly limitation in peripheral vascular function may be encountered among adult males without clinically demonstrable disease.

Represents an aid to the diagnosis of peripheral vascular disease. Provides a critical evaluation of the use and limitations of secondary indices of circulatory function.

Proposed course of project: Skin cooling rate curves will be analyzed to see if the age differences in temperature are related to demonstrable differences in heat regulation.

Venous occlusion plethysmography will be used to estimate peripheral circulation under various conditions of "maximal" vasodilation. "Minimal" peripheral resistance and the changes induced in resistance are to be studied in relation to alterations of arterial pressure.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-99C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	16,600	2	2	4	.83	2.00	2.83
FY 1956	16,600	2	2	4	.83	2.00	2.83

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals

14. None.

R.D.C. -- 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-99C
SERIAL NO.

16. None.

17. None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-100C
SERIAL NO.
6. Age Changes in Renal Physiology.
PROJECT TITLE
7. N. W. Shock (1/4 time)
PRINCIPAL INVESTIGATOR(S)
8. C.O. F. A. Silverstone (1/2 time) and GS-11 Biochemist (Yiengst - 1/2 time)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The objectives of this project are to describe the effects of aging on renal function. Age differences in the ability of the kidney to excrete various substances and to re-adjust blood composition when experimental displacements are induced are under investigation. The effects of age on renal responses to various drug and endocrine products are also being investigated.

Methods employed: Standard clearance methods for estimating GFR, renal plasma flow and T_m are used. In addition, analyses of blood and urine for other substances under study such as vitamin B₁₂, ammonia, acidity, and other electrolytes are carried out under conditions of experimental administration of these substances as well as during acid and alkali loading.

Studies on renal tissue from rats of various ages are also being investigated by the Warburg technique.

Major findings: Determinations of T_m diodrast and T_m PAH have been made on the same subject. The ratio of T_m diodrast/ T_m PAH is approximately 2.5 and does not change with increasing age.

Renal clearance of vitamin B₁₂ has been determined at a number of plasma levels. When the B₁₂ concentration in the plasma is greater than 1 milli gamma per cc., the amount of B₁₂ excreted is dependent on the GFR. No evidence for a T_m for B₁₂ was found.

Preliminary results on the oxygen uptake of kidney slices from young and old rats have been completed. Although the oxygen uptake, per unit wet weight diminishes with age, this difference disappears when computations are based on nitrogen or DNA content of the slice.

Increase protein intake in 8 aged males resulted in a small increase in GFR and renal plasma flow but was without effect on T_m PAH.

Significance to heart research: The incidence of renal disease increases with age. Consequently it is important to identify changes in renal function that may occur with age prior to the development of clinically identifiable renal disease. Knowledge about age changes in renal mechanisms is necessary for the development of rational methods for the prevention and treatment of kidney disease.

Proposed course of project: This laboratory has defined the age changes in renal blood flow, GFR and T_m . However, other important renal processes, such as the excretion of ammonia and the adjustment of pH of the blood in the presence of acid or alkali loading remain to be investigated. These processes are of primary importance in daily living. Consequently, experimental displacements of the acid base balance of the blood will be induced and the responses of the kidney will be measured in terms of ammonia excretion, and titratable acidity.

In addition, experiments on kidney slices and homogenates from young and old rats will be continued. The succinoxidase system will be investigated as well as age differences in the capacity of kidney slices to concentrate PAH.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-100C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	13,300	3	1	4	1.33	1.00	2.33
FY 1956	13,300	3	1	4	1.33	1.00	2.33

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals

14. None.

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-100C
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING
CALENDAR YEAR 1954:

Miller, J. H., and H. D. Bogdonoff: Antidiuresis Associated with
Administration of Insulin. J. Appl. Physiol., 6: (3), 509-512,
Feb. 1954.

17. None.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-101C
SERIAL NO.
6. Pulmonary Physiology as Related to Age.
PROJECT TITLE
7. A. H. Norris (1/2 time) and C.O. - J. A. Falzone (1/3 time)
PRINCIPAL INVESTIGATOR(S)
8. None.

9. PROJECT DESCRIPTION:

Objectives: To describe age changes in pulmonary function. These studies involve measurements of the volumes of lung compartments, the functional capacity of the pulmonary system, including mechanical aspects of bellows function and the responsiveness of the respiratory to experimental stimulation and displacement.

Methods employed: In addition to the standard methods of measuring respiratory volumes a helium washout technique has been devised to give estimates of functional volumes as well. An attempt to relate anatomical measurements made directly on the chest, as well as roentgenographic measurements, including motion of the diaphragm, with functional measurements is being made. In addition, the laboratory measurements are being correlated with clinical estimates of pulmonary function. The responses to experimentally administered CO₂ are also being measured.

Major findings: The first part of this study requires measurements on a large series of subjects between the ages of 20 and 95. During the past year over 100 subjects were studied, but a total of approximately 150 are required for the completion. Preliminary analysis of the data show significant decrements in vital capacity and voluntary ventilatory capacity, but only slight reductions in residual volume.

Administration of 6% CO₂ has been carried out in a small series of experiments. In a few of the older subjects, rigidity of the chest cage may be a factor in limiting the maximum ventilation, but it is not the limiting factor in all the aged subjects tested. There is no evidence of an age difference in sensitivity to CO₂ or the rise in blood pressure induced by CO₂ administration. The metabolic cost of the increment in ventilation was 1.0 cc. oxygen per liter of excess ventilation.

Significance to heart research: Prevention of the increased incidence of chronic pulmonary disease in elderly people requires knowledge about age changes in pulmonary function. Previous investigations from this laboratory have shown that older subjects increase their respiratory volume much more than do young subjects when a standard exercise is performed, even when the oxygen requirements for the work are the same. Hence, studies of pulmonary volume, dead spaces, and rates of transfer of gases across the alveolar membrane are of fundamental interest.

Proposed course of project: Additional subjects will be tested by procedures presently available. In addition, studies of age changes in the elastic properties of the intact lung will be attempted. Since aging is accompanied by a loss of tissue elasticity, measurements on the lung may afford a useful index of physiological age.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 101C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	11,600	2	1	3	.83	1.00	1.83
FY 1956	11,600	2	1	3	.83	1.00	1.83

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL- 101C
SERIAL NO.

16. None.

17. None.

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE

2. Gerontology
LABORATORY OR BRANCH

4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)

5. NHI-102C
SERIAL NO.

6. Age Changes in Metabolism and Endocrine Function.
PROJECT TITLE

7. N. W. Shock (1/4 time)
PRINCIPAL INVESTIGATOR (S)

8. C.O. - S. P. Baker and C.O. - F. A. Silverstone (1/2 time).
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The objectives of this project include a description of age changes in metabolism, a characterization of the nutritional requirements of aging people and a description of age changes in the functional capacities of the endocrine glands. Investigations of calcium and protein requirements of aged males and the effects of various steroid hormones on metabolic balances are in progress. In addition to descriptions of overall metabolism, investigations of special aspects of carbohydrate metabolism as well as age differences to response to insulin are being made. Studies on the functional capacities of specific endocrine organs, such as the thyroid.

Methods employed: For studies on nutritional requirements and the metabolic effects of steroid hormones on eight bed metabolic balance ward, with a special kitchen for food preparation and laboratories for the chemical analysis of foods, urine and stools has been established. Patients from the research ward of the Section (located in

the Baltimore City Hospitals) are observed under rigorously controlled conditions for periods of 3-6 months during which time dietary intakes of Ca, N, etc. are systematically varied, or various steroid hormones are administered. Studies of age differences in lipid metabolism, as well as carbohydrate utilization are carried out. For the latter, the intravenous glucose tolerance test, both with and without the simultaneous administration of known amounts of insulin, is utilized. Estimates of thyroid function include determinations of basal oxygen consumption by the open circuit method, and the rate of uptake of I^{131} by the thyroid gland. Estimates of fluid compartments utilize thiocyanate (for extra cellular fluid volume) and anti-pyrene (for total body water).

Major findings: It has been found that although the basal oxygen consumption per unit of surface area diminishes with increasing age in males, there is no significant age change when the oxygen consumption is calculated per liter of body water. It was also shown that aged males retain their ability to store calcium, nitrogen, potassium and phosphorus and to form new protoplasm when the protein and calcium intake is increased. Administration of steroid hormones (stilbestrol or androstanolone) will further enhance the retention of nitrogen. Studies on blood cholesterol and serum lipoproteins show a relatively high variation from day to day in the same person. With increasing age, the rate of decline of blood sugar levels resulting from the administration of insulin diminishes. Thus the old individual does not respond to insulin as efficiently as does the young.

Significance to heart research: At present the dietary requirements of elderly people are largely inferred from studies made on young adults. With the increasing number of the aged in our population it is essential that we learn something about the basic dietary requirements of the group. Many of the phenomena of aging bear a superficial resemblance to endocrine deficiencies. It is important to find out the extent to which the fundamental metabolic processes change with age and the influence of various hormones on these phenomena.

Proposed course of project: Further studies on the effects of alterations in fat content of the diet on the retention of nitrogen, calcium, phosphorus and potassium are planned. The studies on basal metabolism as related to body water content will be extended to females to see whether the sex difference in metabolic rate remains. Studies of the functional capacity of the thyroid gland as well as the response to administered thyroid substances will be carried out.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-102C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	39,900	3	6	9	1.50	5.00	6.00
FY 1956	44,600	3	8	11	1.50	7.00	8.50

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals

14. None.

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-102C
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Watkin, D. M., E. Y. Lawry, G. V. Mann and M. Halperin: A Study of Serum Beta Lipoprotein and Total Cholesterol Variability and its Relation to Age and Serum Level in Adult Human Subjects. J. Clin. Invest., 33: (6), 874-883, June 1954.

Dogdonoff, M. D., N. W. Shock and J. Parsons: The Effects of Stilbestrol on the Retention of Nitrogen, Calcium, Phosphorus and Potassium in Aged Males With and Without Osteoporosis. J. Geront., 9: (3), 262-275, July 1954.

Shock, N. W.: Some Physiological and Biochemical Aspects of Aging. In: Symposium on Problems of Gerontology. The National Vitamin Foundation, Inc., N. Y., Nutrition Symposium Series, No. 9, August 1954, pp. 1-23.

Shock, N. W., and M. J. Yiengst: Age Changes in Basal Respiratory Measurements and Metabolism in Males. J. of Geront., 10: January 1955.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

N. W. Shock was awarded an honorary degree (Doctor of Science) by Purdue University, May 30, 1954 for "contributions to the field of gerontology."

Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-1030
SERIAL NO.
6. Age Changes in Cellular and Tissue Physiology.
PROJECT TITLE
7. N. W. Shock (1/4 time)
PRINCIPAL INVESTIGATOR (S)
8. GS-9 Biochemist (Barrows and GS-11 Biochemist (Ylengst - 1/2 time)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The objectives of this project are to investigate age changes in the chemical composition of tissues and alterations in enzyme activity of tissues, cells and their components. A primary goal of the project is to develop an index of the number of functioning cells that are present in a tissue.

Methods employed: These experiments will be carried out initially on slices and homogenates prepared from various tissues of young and old rats. The Warburg technique will be used for determinations of oxygen uptake. Standard methods of enzyme chemistry will be used for other systems, such as the succinoxidase system. In addition, chemical analyses for DNA, RNA, nitrogen, protein, and electrolytes will be made.

Major findings: Preliminary results have been obtained on twelve 30 month old rats and twelve 9 month old rats. In this series there was no evidence of any age change in the resting oxygen uptake of liver or brain. The kidney slices showed some evidence of a reduction in resting oxygen uptake when calculated on the basis of wet weight, but not when calculated on the basis of a nitrogen or DNA content of the sample. The tissues stimulated by the addition of succinate indicated a greater increase in oxygen uptake in young than in old tissues from brain and kidney, but not liver. A marked reduction in the succinoxidase activity of heart tissues from old animals was found. Chemical analyses of muscle tissue indicated an increase in extracellular water and loss of cells although the total water content of this tissue did not diminish in old animals.

Significance to heart research: These studies attempt to examine the aging process at a tissue and cellular level. Since the loss of cells of various tissues is a primary factor in the reduction in reserve capacities of various organ systems that occurs with age, it is important to determine what functional changes occur that prevent individual cells from maintaining their existence. It is also important to know whether these changes are a fundamental characteristic of the cell or whether it is secondary to circulatory impairments in aging animals.

Proposed course of project: The preliminary studies reported above will be repeated on larger groups of animals as they become available. In addition, other enzyme systems will be explored. Histological sections of all tissues studied will be examined by the Pathology Department of the Baltimore City Hospitals (Dr. A. Pollak).

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-1030
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	28,300	3	4	7	1.83	3.00	4.83
FY 1956	28,300	3	4	7	1.83	3.00	4.83

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Dr. A. Pollak, Pathologist, Baltimore City Hospitals; Dr. Bacon F. Chow, Johns Hopkins University School of Public Health.

14. None.

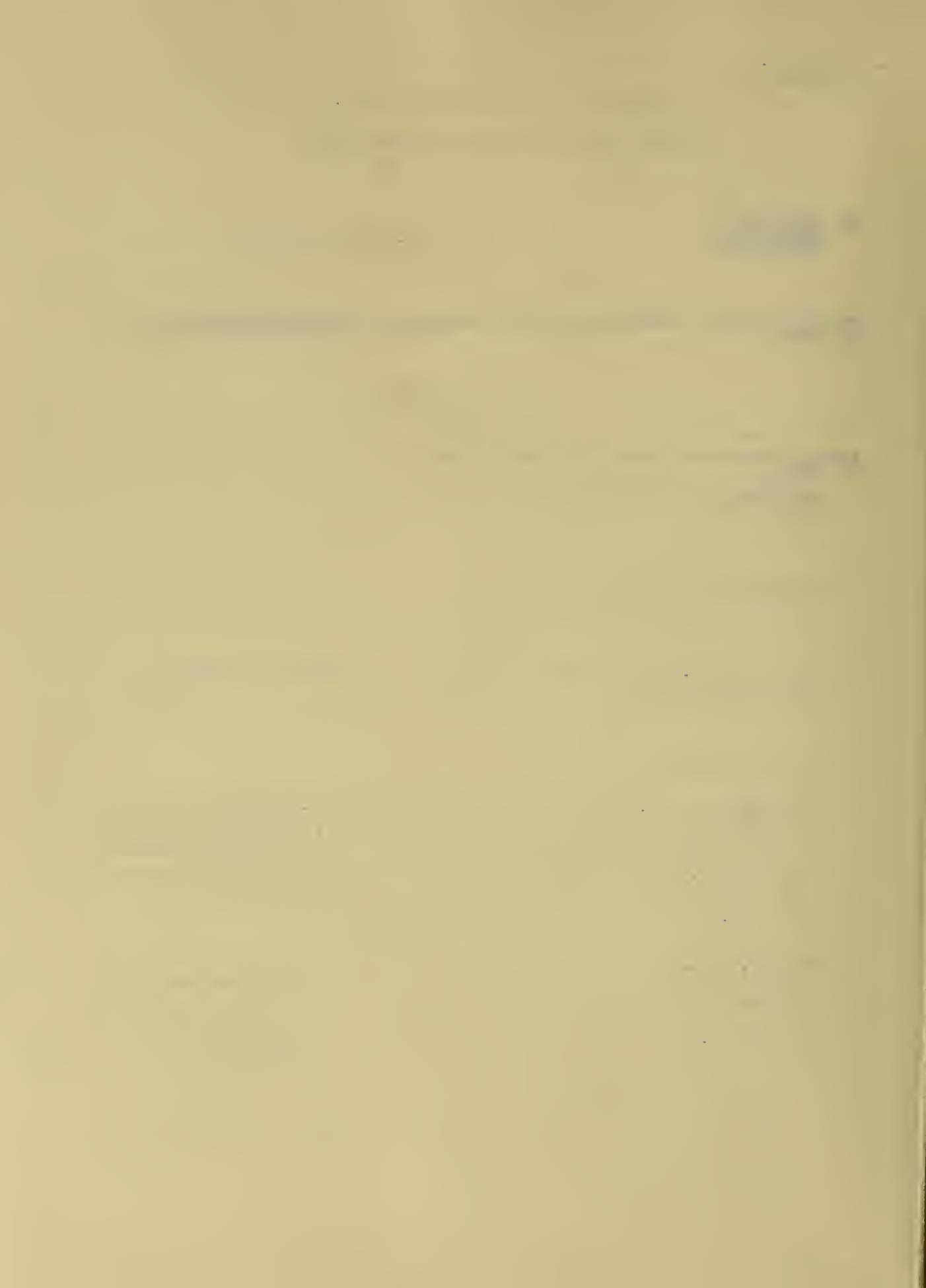
R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-103
SERIAL NO.

16. None.

17. None.



Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHL-104C
SERIAL NO.

6. Age Changes in Human Performance.
PROJECT TITLE

7. N. W. Shock (1/4 time)
PRINCIPAL INVESTIGATOR(S)

8. C.O.-A. H. Norris (1/2 time) and C.O.-J. A. Falzone (1/3 time)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: This project is designed to study the effects of aging on (a) the physiological responses to exercise, (b) the rate of recovery of physiological equilibrium after exercise, (c) muscular efficiency and (d) work output and fatigue. In addition, the factors responsible for limitations in performance observed in older people will be evaluated.

Methods employed: Measured amounts of physical work will be obtained in subjects of varying ages by means of a calibrated arm ergometer and a treadmill. Measurements of oxygen uptake, CO₂ production, respiration rate, heart rate, blood pressure and cardiac output (by the dye method) will be taken before, during and after standardized amounts of exercise. Each experiment involves chemical analysis of 20-25 samples of expired air. Other studies will include measurements of the speed of nerve conduction, reflex delay time, and muscle action potentials. These phenomena will be recorded from micro electrodes and observed on an 8 channel electroencephalograph or on the dual beam oscilloscope as the experiment demands.

Major findings: Previous studies have indicated that the oxygen required per unit of external work is not significantly increased in aged males. However, the older subjects require a much greater increase in ventilation volume to provide a given level of oxygen uptake during exercise than do young subjects. During the past year, approximately 60 subjects between the ages of 20 and 90 years have been tested at three different levels of work output. For completion, this study will require an additional 50 or 60 subjects. These experiments will provide data for estimating age differences in mechanical efficiency as well as differences in rate of recovery of ventilation volume, oxygen uptake, CO₂ elimination, heart rate and blood pressure. Instrumentation for the study of age changes in neuro-muscular performance has been assembled and subjected to preliminary tests.

Significance to heart research: The effect of age on human performance is of importance both to industry and medicine. With the increasing number of elderly workers in our population, industry is concerned with the question of retirement and has expressed a need for objective methods to determine individual retirement. In medicine, the question of the degree of activity that can be permitted elderly patients with varying degrees of cardiovascular disease is of practical importance. This program represents an attempt to provide base line data, but also looks to the development of reliable tests that can be applied to large numbers of subjects. In addition, specific knowledge about the effect of age on performance will increase our understanding of aging in the human.

Proposed course of project: The survey of individual differences in responses to standardized amounts of physical exercise will be continued, with the addition of estimates of cardiac output in selected subjects. Studies on the relationship between oxygen uptake and heat production will be carried out in collaboration with the cooperative study of Human Performance sponsored by the Physiology Study Section. Studies of age differences in neuro-muscular function will be initiated. These studies will attempt to discover the physiological locus of the observed slowing in speed of response that occurs with increasing age.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-104C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	30,000	3	4	7	1.17	4.00	5.17
FY 1956	30,000	3	4	7	1.17	4.00	5.17

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956:

Baltimore City Hospitals, Naval Medical Research Institute - cooperative project on Human Performance sponsored by the Physiology Study Section.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-104C
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING
CALENDAR YEAR 1954:

Norris, A. H., N. W. Shock and M. J. Yiengst: Age Differences in
Ventilatory and Gas Exchange Responses to Graded Exercise in Males.
To be published in the April issue of the J. of Geront.

17. None.

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Analysis of NIH Program Activities

Project Description Sheet

1. Heart
INSTITUTE
2. Gerontology
LABORATORY OR BRANCH
4. Baltimore City Hospitals
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-105C
SERIAL NO.

6. Psychological Aspects of Aging.
PROJECT TITLE

7. GS-13 Psychologist
PRINCIPAL INVESTIGATOR(S)

8. None.

9. PROJECT DESCRIPTION:

Objectives: The objectives of this program are to describe the psychological changes that occur in aging people with particular reference to intellectual and emotional responses and their relationship to physiological processes.

Methods employed: Standard psychological tests of mental performance, learning ability, perception and emotional reactions will be employed. Examples are the Thurstone test of Primary Mental Abilities, the Wechsler-Bellevue Adult Intelligence test, the Babcock Efficiency Index, the Bills test of perceptual blocking, galvanic skin reflex, tachistoscopic learning tests, and the electro-encephalograph. Additional tests will be designed and standardized as needed.

Subject material: In addition to patients in the Infirmary Division of the Baltimore City Hospitals, subjects still living in the community will be studied. For this purpose arrangements for testing all employees in a large industry in Baltimore will be made.

Major findings: Since the position of psychologist has been available only since July 1, 1954, no work in this area has been completed during the present year. Previous studies from this laboratory have demonstrated age changes in visual perception, adaptation of the eye to night vision, differential effects of age on mental performance and an analysis of age changes in the speed of response in both mental and psycho-motor tasks.

Significance to heart research: The psychological characteristics of aging people must be known if we are to make sensible recommendations with regard to retirement policies and plan effective programs for the utilization of the capacities of older people in our population. The fundamental scientific problem of psychological aging is the identification of the factors which contribute to psychological deterioration. To prevent psychological deterioration it is necessary to know what portion is the result of physiological factors such as blood flow to the brain, intrinsic alterations in cellular metabolism, altered permeability of blood vessels, altered characteristics of nerve cells and psychological factor such as inhibition of learning, functional disuse atrophy alterations in motivation or emotional responses to the environment. Hence, effective psychological studies require parallel physiological and medical investigation.

Proposed course of project: Direction of the immediate studies will depend in part on the specific interests of the psychologist being recruited.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-105C
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	0	0	0	0	0	0	0
FY 1956	7,000	1	0	1	1	0	1

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. None.

14. None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-105C
SERIAL NO.

16. None.

17. None.

R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Cardiovascular Hemodynamics
LABORATORY
5. NHI-106
SERIAL NO.
6. Permanent By-Pass of the Aortic Valve
PROJECT TITLE
7. Stanley J. Sarnoff, M.D.
PRINCIPAL INVESTIGATOR
8. Robert B. Case, M.D.
OTHER INVESTIGATOR

PROJECT DESCRIPTION

Objectives: To ascertain whether, by providing an avenue of egress for left ventricular blood via the apex to thoracic aorta, a means can be devised for the alleviation of aortic stenosis.

Major Findings: It is clear that this procedure can be done successfully and when it is successful the dogs so treated are competent and vigorous even though the ascending aorta is completely occluded. The valve shortens the half-life of dog red cells considerably, but this is, in most large dogs, compensated for by increased erythropoietic activity.

Proposed Course of Project: Investigation of means whereby the procedure can be done successfully and consistently; further investigation of red cell damage in dog and man.

Significance: If this procedure can be applied to man, a more effective means of alleviating aortic valvular disease will be at hand than is currently available.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-106
SERIAL NO.

11. BUDGET DATA

	Estimated Expenditures	Position			Man Years		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	11,200	2	3	5	.33	1.17	1.50
FY 1956	16,200	2	5	7	.33	3.17	3.50

12. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION
REVIEW & APPROVAL		TECHNICAL ASSISTANCE

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-106
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Cardiovascular Hemodynamics
LABORATORY

5. NHI-107
SERIAL NO.

6. Positive Pressure Breathing
PROJECT TITLE

7. Stanley J. Sarnoff, M.D., Robert B. Case, M.D.
PRINCIPAL INVESTIGATORS

8. John T. Binion, M.D., William L. Morgan, Jr., M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To ascertain whether an appropriate pharmacologic intervention can diminish or delay the adverse effects of high levels of positive pressure breathing.

Methods: Electrical recording of airway, atrial and arterial pressures.

Major Findings: After three preliminary or pilot experiments, four informative experiments in dogs were performed. From these it was clear that, in a dog brought to almost complete circulatory standstill by high levels (50-60 mm Hg) of PPB, a pharmacologic intervention was capable of restoring circulation for a period of 35 to 70 minutes (average - 51 minutes) thereafter while the original high level of PPB was maintained.

Significance: The data available suggest that we have at hand a means of favorably affecting the circulation depressed by high levels of PPB. Fluoroscopic motion pictures taken during PPB also reveal the anticipated importance of cardiac tamponade in this situation.

Proposed Course of Project: Amplification and variation of conditions in above experiments.

Budget Data Sheet

10. NHI --107
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Position			Man Years		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	18,100	4	2	6	1.67	.83	2.50
FY 1956	18,100	4	2	6	1.67	.83	2.50

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-107
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Cardiovascular Hemodynamics
LABORATORY

5. NHI - 108
SERIAL NO.

6. Circulatory Derangements In Hemorrhagic Shock
PROJECT TITLE

7. John T. Binion, M.D., William L. Morgan, Jr., M.D., Stanley J. Sarnoff, M.D.
PRINCIPAL INVESTIGATORS

8. None

9. PROJECT DESCRIPTION

Objectives: (a) To ascertain whether the use of sympathomimetic pharmacologic interventions made during the phase of oligemic hypotension can confer any protection on dogs so treated. (b) To find out whether it is possible to restore the pressor response to such medication in shocked dogs who have lost this response due to oligemic hypotension.

Major Findings: (a) It has been ascertained that Aramine (a long-acting, norepinephrine like compound) does reduce the mortality of dogs subjected to control shock conditions. Ninety dogs have been studied in this group. The first ten were pilot or standardizing experiments. The remaining eighty comprised 40 sets of control and treated dogs. In the last group of 20 sets, the survival rate of the treated group was twice that of the control group. (b) Only four experiments have been done to ascertain whether hydrocortisone or 9- α -fluorohydrocortisone will restore the pressor response to norepinephrine and Aramine. The data thus far are too meager to permit of conclusions.

Proposed Course of Project: Amplification of work under 2(b) above.

Significance: These findings may a) throw light on the nature of the circulatory derangement that occurs after prolonged periods of a depressed circulation and b) have therapeutic implications.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 108
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Position		Total	Man Years		
		Prof.	Other		Prof.	Other	Total
FY 1955	16,300	3	2	5	1.33	.83	2.17
FY 1956	16,300	3	2	5	1.33	.83	2.17

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-108
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Cardiovascular Hemodynamics
LABORATORY

5. NHI-109
SERIAL NO.

6. Heart Valve Study
PROJECT TITLE

7. Ian K. R. McMillan, M.B.
PRINCIPAL INVESTIGATOR

8. None

9. PROJECT DESCRIPTION

Objectives: a) A more precise understanding of valve mechanisms
b) To ascertain the functional effect of therapeutic procedures aimed at diminishing valve dysfunction.

Methods Employed: Human hearts obtained at post-mortem are mounted in a perfusing chamber in which the pressure gradients, pulse rates and flows can be regulated at will and measured.

Major Findings: None thus far. The apparatus for doing this study has just been completed. It is expected that it will be "debugged" and photography of functioning heart valves will be begun in February.

Significance: From previous studies of the same sort it is expected that the objectives as outlined above may be realized.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 109
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Position		Total	Man Years		
		Prof.	Other		Prof.	Other	Total
FY 1955	6,000	1	1	2	.50	.33	.33
FY 1956	12,000	2	1	3	1.50	.33	1.33

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-109
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Cardiovascular Hemodynamics
LABORATORY

5. NHI-110
SERIAL NO.

6. Hypothermia
PROJECT TITLE

7. Ian K. R. McMillan, M.B., Robert B. Case, M.D., Stanley J. Sarnoff, M.D.

8. None

9. PROJECT DESCRIPTION

Objectives: To ascertain whether myocardial hypoxia plays a significant role in the genesis of ventricular arrhythmias seen during hypothermia.

Methods Employed: Continuous electrical recording of right and left atrial and femoral arterial pressures, and pulse rates along with total left main coronary flow (rotameter). Cooling by "vascular coil" through and icewater bath.

Major Findings: Only three experiments have been completed. Although much too early to tell, the data thus far available do not support the view that myocardial hypoxia is present.

Proposed Course of Project: Limited to confirmation of the above information.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 110
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Prof.	Position		Man Years		
			Other	Total	Prof.	Other	Total
FY 1955	10,100	3	2	5	.33	.34	1.67
FY 1956	18,500	4	3	7	1.33	1.84	3.67

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

R P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-110
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Laboratory of Cardiovascular Hemodynamics
LABORATORY

5. NHI-111
SERIAL NO.

6. Smooth Muscle Tone
PROJECT TITLE

7. Edward J. Leonard, M.D.
PRINCIPAL INVESTIGATOR

8. None

9. PROJECT DESCRIPTION

Objectives: The objective of the project is to work out a system for maintaining a section of isolated blood vessel in a viable state in an artificial medium, and then to measure the capacity for this vessel to develop tension under a variety of physiological conditions.

Methods Employed: A section of the carotid artery of a rabbit is carefully isolated from the tissues which surround it and is removed to an oxygenated bath of Krebs-bicarbonate solution. The vessel is then cannulated at each end, and is filled with oil so that the artery may contract against a fluid-filled system, which is connected to a pressure transducer of small volume displacement. The magnitude of the essentially isometric contraction which occurs after appropriate stimulation (for example, by adding epinephrine in small concentration) is recorded on a direct writing oscillograph.

Major Findings: The major findings of the project during the first two months has been that it is possible to maintain an isolated vessel in Krebs-bicarbonate solution so that viability, as measured by the magnitude of contractile response to a standard adrenalin stimulus, is reasonably constant over a period of several hours. It appears, therefore, that it will be possible to get a stable preparation for physiological study.

Significance: The present study was prompted by the question as to whether

the increased peripheral vascular tone in essential hypertension is caused not by some abnormal circulating vasoactive substance, but rather by an increased reactivity of the vessels to normally occurring vasopressor agents. It is possible, for example, that the reactivity of vascular smooth muscle is dependent on intra-cellular cations, the level of which is regulated by certain blood borne agents. As a first approach to this problem it seems appropriate to study isolated vessels which are removed from nervous and hormonal influences - to determine what chemical factors affect blood vessel tone. This may provide some clues to the question of what causes abnormalities in arteriolar tone in human disease.

Proposed Course of Research: The central problem in the initial phases of this study is to determine the best set of conditions for maintaining an artery in a viable state. The type of artery to study, methods of dissection, composition and temperature of the bathing medium, nourishment of the vessel from the luminal or adventitial side -- are the kinds of questions that need to be answered. Following this, the response of the vessel to a variety of known vasoactive agents will be investigated. Then a study will be made on what factors alter the response to these agents. The usefulness of the system as a bioassay tool for detection of circulating substances which might alter reactivity of blood vessels may eventually be explored.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 111
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Position			Man Years		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	9,700	1	0	1	1.00	0	1.00
FY 1956	9,700	1	0	1	1.00	0	1.00

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 111
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Position			Man Years		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	9,700	1	0	1	1.00	0	1.00
FY 1956	9,700	1	0	1	1.00	0	1.00

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 111
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute 2. Laboratory of Cardiovascular Hemodynamics

5. NHI-112
SERIAL NO.

6. A Study of Peripheral Hemodynamics
PROJECT TITLE

7. Robert P. Akers, Ph.D.
PRINCIPAL INVESTIGATOR

8. None

9. PROJECT DESCRIPTION

Objectives: A. To improve the present method of preparation and maintenance of the vascular bed of the hamster cheek pouch so as to be able to study the circulation in an as normal state as possible. B. To further explore the value of the hamster cheek pouch as a bioassay "tool" for the quantitative determination of effective constrictor properties of various biological substances such as blood plasma.

Methods Employed: Preparation of the hamster cheek pouch for direct visualization of the peripheral circulation is according to the method of Lutz, Fulton, and Akers. Major improvements have been made in this technique by using a continuous perfusion over the preparations and by using well oxygenated (95% O_2 , 5% CO_2) Krebs-bicarbonate solution instead of mammalian Ringers or Ringer-gelatine as previously used.

Major Findings: The major findings over the past year have been the determination of the high degree of sensitivity of the arteriolar elements of the hamster cheek pouch to topically applied vasoconstrictor substance (epinephrine 0.0001 to 0.001 μgm per ml). This epinephrine sensitivity has formed the basis for bioassay for vasoconstrictor substances contained in blood plasma. The vasoconstrictor substance for blood plasma is recorded in constrictor properties equivalent to that amount of epinephrine to produce a similar reaction. Human blood plasma assayed by this technique, has from 10 to 30 μgm per liter epinephrine constrictor units.

Significance: The hamster cheek pouch technique makes possible a rapid method for the bioassay of constrictor substances in blood plasma.

The constrictor properties can then be expressed in a quantitative manner in terms of epinephrine producing a like reaction. Such a bioassay technique appears to be useful in the study of hypertension, shock, sickle cell anemia and possibly in many other diseases.

Proposed Course of Project: A. Study of the effects of temperature, pH, and cation concentration of perfusion media upon normal circulation. B. Continue to develop the hamster cheek pouch technique for bioassay purposes and to characterize the plasma constrictor factors by pharmacological and chemical procedures.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI - 112
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Position			Man Years		
		Prof.	Other	Total	Prof.	Other	Total
FY 1955	14,700	1	1	2	1.00	1.00	2.00
FY 1956	14,700	1	1	2	1.00	1.00	2.00

12. BUDGET ACTIVITY:

RESEARCH

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI - 112
SERIAL NO.

16. None

17. None

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO: NIH-113
6. PROJECT TITLE: Isolation of Physiologically Active Agents from Plants.
7. PRINCIPAL INVESTIGATOR: Mr. D. L. Rogerson
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objectives:

This project involved the examination of crude plant materials by means of chemical and physiological procedures in order to detect physiologically active agents. When these were found, suitable isolation procedures, on a large or small scale, were carried out to obtain the active material.

Methods employed:

Qualitative and quantitative estimations of alkaloids were arrived at by conventional methods, modified as necessary for the specific cases under study. The acute effects of extracts and of alkaloidal fractions were studied (generally in dogs) and where further investigation was indicated large or moderate scale isolation procedures were developed.

Major Findings:

A process for the isolation of andromedotoxin from Rhododendron maximum leaves was developed and applied on a scale sufficient to supply material for pharmacological, chemical, and clinical investigation. This substance is a potent hypotensive agent whose action resembles that of protoveratrine; it is currently being studied clinically in the General Medicine Branch of NIH.

An investigation of seeds of Piptadenia peregrina led to the isolation and study of several indole derivatives. Chemical work on P. peregrina alkaloids and related compounds is still in progress. The isolation of bufotenine from this source stimulated clinical investigation (in NIMH) of its effects in humans.

A potent hypotensive agent of unknown structure has been isolated from seeds of a tropical plant. Current work (in the Laboratory of Chemical Pharmacology, NIH) indicates that the substance is a vasodilator acting through the central nervous system.

A number of Amaryllidaceae alkaloids were isolated for chemical and pharmacological work. These alkaloids are under intensive study in this Laboratory.

TO THE HONORABLE MEMBERS OF THE HOUSE OF REPRESENTATIVES
IN SENATE CHAMBERS
WASHINGTON, D. C.
JANUARY 10, 1910

DEAR SENATORS:

I have the honor to acknowledge the receipt of your letter of the 7th inst. in relation to the proposed amendment to the Constitution of the United States, which provides for the election of Senators by the people.

I am sorry to hear that you are dissatisfied with the proposed amendment, and I am sure that you will be able to present your views on this subject in a most effective manner at the coming session of the Senate.

I am, Sir, very respectfully,
Your obedient servant,
W. W. BROWN,
Secretary of the Senate.

I am, Sir, very respectfully,
Your obedient servant,
W. W. BROWN,
Secretary of the Senate.

I am, Sir, very respectfully,
Your obedient servant,
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I am, Sir, very respectfully,
Your obedient servant,
W. W. BROWN,
Secretary of the Senate.

Significance to Heart Research:

This work is concerned with the initial phases of detection, isolation, and study of complex natural substances which affect the circulatory system. Some of these substances, which usually can be isolated only with difficulty, are potential therapeutic agents. In these cases the isolation work is followed by study along chemical, pharmacological, and clinical lines. Hypotensive agents, for example, are under particular study. Of possibly even greater importance is the fact that these natural materials are of value in providing a means of studying physiological phenomena involving the circulatory system. For example, the hypotensive agent of unknown structure found during the close of the year does not completely correspond in its mode of action to any previously known substance.

Proposed Course of Project:

Substances under active chemical, pharmacological, or clinical study will be isolated in sufficient quantity to support the studies. New procedures will be required for several of these, and a considerable amount of development work will be necessary. Exploratory work on new plant materials will be continued. A joint program of study on Puerto Rican plants has been initiated with the Federal Agricultural Station at Mayaguez, P.R. This will be continued through most of the calendar year 1955.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-113
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	34,700	1	4	5	1	4	5	
FY 1956	36,300	1	4	5	1	4	5	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1

Section of Plant Introduction, Agricultural Research Service.

U. S. Dept. of Agriculture

Section on Fractionation and Isolation, Laboratory of Biochemistry
and Nutrition, NIAMD

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 113

16. None

17. None

R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO.: NHI - 114
6. PROJECT TITLE: Alkaloids of Ochrosia elliptica
7. PRINCIPAL INVESTIGATORS: Dr. S. M. Goodwin
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

The isolation, characterization, and structural determination of the alkaloids of Ochrosia elliptica.

Methods employed:

Small-scale isolation procedures were studied and modified for this problem. Instrumental and analytical data provided preliminary information about the alkaloids, and degradation studies are now in process.

Major Findings:

Three new alkaloids were isolated from leaves of Ochrosia elliptica. Their empirical formulas were determined, and structures have been proposed in part for all three.

Significance to Heart Research:

The plant from which these alkaloids are derived is in the Apocynaceae family. This family includes the Rauwolfia group, and hypotensive and tranquilizing substances may be expected to occur through this group. Other plants in this family are also under investigation.

Proposed Course of Project:

Degradation work on these alkaloids will be continued. The synthesis of selected ring systems will be required for comparisons of physiochemical properties.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 114

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$7,800	1	1	2	.50	.50	1.00	
FY 1956	14,800	2	2	4	.83	.84	1.67	

12. BUDGET ACTIVITY:

- RESEARCH
- ADMINISTRATION
- REVIEW & APPROVAL
- TECHNICAL ASSISTANCE

13. None

14. None

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R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. SERIAL NO: NHI - 114

16. None

17. None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO: NHI-115
6. PROJECT TITLE: Rearrangements Leading to Oxindoles or Related Compounds
7. PRINCIPAL INVESTIGATOR: Dr. H. A. Lloyd
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

Rearrangements involving changes in ring size are frequently important in the chemistry of heterocyclic systems. A study of a specific type of amide-ester rearrangement leading to oxindoles and related compounds was carried out.

Methods employed:

New products resulted from the application of exchange conditions to certain amide-esters. The structures of these compounds were proved by a combination of instrumental and synthetic studies.

Major findings:

The existence of a suspected rearrangement was confirmed by a chemical study of the compounds involved.

Significance to Heart Research:

These studies may be useful in interpreting the chemistry of certain nitrogen-containing heterocyclic systems. They are of value largely as new information in this field of chemistry.

Proposed Course of Study:

This project has been completed.

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Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 115

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$7,700	1	1	2	.84	.33	1.17	
FY 1956	0	0	0	0	0	0	0	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

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R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

5. SERIAL NO.: NHI - 115

6. PUBLICATIONS:

"Synthesis of Oxindole-3-propionic Acid by Ring Rearrangement".
By H. A. Lloyd and E. C. Horning. J. Am. Chem. Soc., 76, 3651 (1954).

7. None



R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Chemistry of Natural Products
3. SERIAL NO.: NIH - 116
6. PROJECT TITLE: Alkaloids of Aristotelia Spp., Siderocarpus Spp., and Related Genera
7. PRINCIPAL INVESTIGATOR: Dr. H. A. Lloyd
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

To isolate, characterize, and determine the structure of the alkaloids of these genera.

Methods employed:

Solvent extraction procedures, chromatography, and related isolation procedures were employed to provide materials for study. Some of these isolation methods are still under study for specific plants. The characterization of each material was initiated by an instrumental study directed to establishing the nature of the functional groups present in the molecule.

Major findings:

The most significant occurrence in this area during the year was the discovery of a new potent hypotensive agent of unknown structure. This substance apparently acts through the central nervous system, and in low doses it produces a marked sustained fall in blood pressure.

Significance to Heart Research:

A study of the action of this compound may provide new information about the physiological phenomena involved in hypertension.

Proposed Course of Study:

Chemical studies on the structure of this material and pharmacological studies on its mode of action will be continued. Other alkaloids isolated from this group of plants will be studied.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 116

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	3,900	1	1	2	.33	.34	.67	
FY 1956	6,900	2	1	3	.83	.34	1.17	

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 116

16. None

17. None

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO: NHI-117
6. PROJECT TITLE: Studies on Molecular Complexes
7. PRINCIPAL INVESTIGATOR: Dr. H. A. Lloyd
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

To study the physical and chemical properties of selected molecular complexes.

Methods employed:

The desired molecular complexes were synthesized by general methods. These are currently under study using chemical and instrumental means.

Major findings:

Emphasis has been given to the study of mixed complexes in relation to the parent symmetrical complexes. It is not yet possible to interpret all of the results.

Significance to Heart Research:

One-electron oxidation reduction is the fundamental reaction by which the transfer of energy is accomplished in biological systems. In this sense, it is responsible for the existence of life processes. It is a phenomenon which is known to involve molecular complexes, but the chemistry of these substances is difficult to study and basic information about the structure and properties of many complexes is lacking.

Proposed Course of Study:

A few experiments remain to be completed. These involve studies of the properties of mixed phenazine complexes. The required materials have been prepared.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-117
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	3,800	1	1	2	.33	.34	.67	
FY 1956	3,800	1	1	2	.33	.34	.67	

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHINICAL ASSISTANCE

13. None

14. None

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R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-117
SERIAL NO.

16. None

17. None

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO.: NHI - 118
6. PROJECT TITLE: Chemistry of Therapeutic Agents
7. PRINCIPAL INVESTIGATOR: Dr. M. S. Fish
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

This project involves cooperative work with the Laboratory of Chemical Pharmacology, NHI, on the structure, synthesis, or degradation of substances of actual or potential therapeutic value. The studies during the past year included investigations on anti-arrhythmic compounds, on synthetic hypotensive agents, and on agents for intravenous anesthesia.

Methods employed:

This work involves synthetic and structure proof studies on selected types of compounds. These included pyridinediones, indazoles, and benzotriazoles.

Major findings:

A new anesthetic agent, effective when given intravenously, was found. Although the compound had the desired short duration of activity, it had a relatively low stability and it is difficult to use.

A new hypotensive agent of moderate activity was found. Since several natural materials were found during the year which were more active, the investigation of synthetics was not expanded.

Significance to Heart Research:

This project is concerned with the synthesis and study of physiologically active agents. Hypotensive agents and anti-arrhythmic agents are among those under study.

Proposed course of study:

New compounds for investigation as potential anti-arrhythmic agents will be prepared. Studies on metabolic transformation products of drugs will be carried on in cooperation with the Laboratory of Chemical Pharmacology, NHI.

THE UNIVERSITY OF CHICAGO
DEPARTMENT OF CHEMISTRY
5800 S. UNIVERSITY AVENUE
CHICAGO, ILL. 60637
TEL. 773-936-3700

RECEIVED
JAN 15 1964

FROM: [Illegible]

TO: [Illegible]

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H. P. C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 118

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$13,500	1	2	3	.50	1.50	2.00	
FY 1956	13,500	1	2	3	.50	1.50	2.00	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

PHYSICS 551

PHYSICS 552

NAME	UNIT NO.	GRADE	MARKS
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PHYSICS 553

PHYSICS 554	PHYSICS 555
PHYSICS 556	PHYSICS 557

PHYSICS 558

PHYSICS 559

R. P. C. - 3
December 1954

Analysis of NHI Program Activities
Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 118

16. None

17. None

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO: NHI-119
6. PROJECT TITLE: Studies on Pinidine
7. PRINCIPAL INVESTIGATOR: Dr. W. H. Tallent
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

An alkaloid of unknown structure was isolated from Pinus sabiniana. This work is directed to a determination of the structure of this substance.

Methods employed:

Degradative studies were employed to provide information about the ring system and substituent groups of this compound. A variety of physicochemical methods were also required for structural diagnostic purposes.

Major findings:

A tentative structure has been proposed for pinidine. The characterization of this alkaloid and the accompanying α -pipecoline was completed. Methods for the study of unsaturation by infrared spectroscopy were developed.

Significance to Heart Research:

New information on the structure of a naturally occurring alkaloid has been obtained. In addition to the progress made on this specific problem, the new diagnostic methods which were studied and developed will be of value in work on other problems of the Laboratory.

Proposed course of project:

The synthesis of the proposed structure will be undertaken as the final stage of proof of structure for the compound.

1. The first part of the document discusses the importance of maintaining accurate records of all transactions.

2. It is essential to ensure that all entries are dated and clearly describe the nature of the transaction.

3. The second part of the document outlines the various methods used to collect and analyze data.

4. These methods include direct observation, interviews, and the use of standardized questionnaires.

5. The third part of the document describes the procedures for ensuring the reliability and validity of the data.

6. This involves careful selection of samples and the use of appropriate statistical techniques.

7. The fourth part of the document discusses the ethical considerations that must be taken into account.

8. These include obtaining informed consent from participants and ensuring the confidentiality of their data.

9. The fifth part of the document provides a summary of the findings and conclusions of the study.

10. It highlights the key results and discusses their implications for future research and practice.

11. The sixth part of the document contains a list of references to the sources used in the study.

12. These references provide a comprehensive overview of the current state of knowledge in the field.

13. The seventh part of the document includes an appendix with additional data and supporting information.

14. This appendix is provided for reference and to allow readers to verify the accuracy of the data presented.

15. Finally, the eighth part of the document contains a list of acknowledgments to those who assisted in the study.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI = 119

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$9,700	1	1	2	.50	1.00	1.50	
FY 1956	11,000	1	1	2	.50	1.00	1.50	

12. BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

13. None

14. None

STATE OF NEW YORK
IN SENATE

January 10, 1907

NAME	RESIDENCE	EDUCATION	PROFESSION
John A.
...
...

...

...

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-119
SERIAL NO.

16. None

17. None

R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO: NHI-120
6. PROJECT TITLE: Metabolites of Butazolidine
7. PRINCIPAL INVESTIGATOR: Dr. S. M. Goodwin
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

The determination of structure and synthesis of butazolidine metabolites.

Methods employed:

Proposed structures for two butazolidine metabolites were arrived at largely by the interpretation of instrumental data. The synthesis of one of these compounds required the development of a route involving a number of chemical steps.

Major Findings:

Structures were proposed for two butazolidine metabolites. The structure of one of them was confirmed by synthesis.

Significance to Heart Research:

Butazolidine is metabolized in humans to at least two products. These were isolated in the Laboratory of Chemical Pharmacology of the National Heart Institute, and their chemistry was studied in this project. The influence of these substances in ionic balance in the body will be studied in the Laboratory of Chemical Pharmacology.

Proposed course of research:

Studies on these metabolites are largely completed.

Analysis of NIN Program Activities

Budget Data Sheet

10. NHI-120
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	7,700	1	1	2	.50	.50	1.00	
FY 1956	4,000	0	1	1	0	.50	.50	

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

13. None

14. None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-120
SERIAL NO.

16. None

17. None

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO.: NHI - 121
6. PROJECT TITLE: Synthesis of Polycyclic Systems Related to
Amaryllidaceae Alkaloids
7. PRINCIPAL INVESTIGATORS: Dr. W. C. Wildman
8. OTHER INVESTIGATORS: Dr. H. M. Fales
9. PROJECT DESCRIPTION:

Objective

The synthesis and structural study of polycyclic systems related to Amaryllidaceae alkaloids.

Methods employed:

The synthesis of complex polycyclic amines of this kind requires extensive chemical research. It is generally necessary to develop new procedures or to modify known methods in order to secure new compounds, and when these materials are obtained physicochemical methods are employed in order to draw structural conclusions or to make structural comparisons.

Major Findings:

The synthesis of a compound possessing the structure first suggested for lycoramine was achieved. As a consequence of this work, together with new data found for lycoramine, it was possible to modify the structure of the alkaloid. New synthetic procedures for the basic systems of these alkaloids were developed.

Significance to Heart Research:

These polycyclic amines have been under intensive study only during the past few years. It is not yet possible to evaluate their usefulness in terms of physiological activity.

Proposed Course of Project:

Attention will be directed to the development of new synthetic approaches to the ring systems of the alkaloids. Current studies will be correlated with work on the degradation of tazattine and other members of the group.

THE UNIVERSITY OF CHICAGO
DEPARTMENT OF CHEMISTRY
58 CHEMISTRY BUILDING
CHICAGO, ILLINOIS 60637

TO: [Name]
FROM: [Name]
SUBJECT: [Subject]

[Text block containing the main body of the letter, including details of the appointment or request.]

[Text block containing the closing of the letter, including a signature and contact information.]

[Text block containing the date and any additional notes or references.]

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 121

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$17,400	2	1	3	1.50	1.00	2.50	
FY 1956	\$17,400	2	1	3	1.50	1.00	2.50	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards and Publications Sheet

15. SERIAL NO.: NHI - 121

16. PUBLICATIONS:

1, 4, 5, 6, 13, 14-Hexahydro-5-methyl-8, 9-methylene-
dioxypheanthridine. By L. H. Mason and W. C. Wildman, J. Am. Chem.
Soc., 76 6194 (1954).

17. None

Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO.: NHI - 122
6. PROJECT TITLE: Structure of Amaryllidaceae Alkaloids
7. PRINCIPAL INVESTIGATOR: Dr. W. C. Wildman
8. OTHER INVESTIGATORS: Dr. R. J. Highet, Dr. L. M. Mason, Dr. E. Warnhoff
9. PROJECT DESCRIPTION:

Objective:

The characterization and determination of structure of Amaryllidaceae alkaloids is the primary objective of this project.

Methods employed:

Studies in the separation and purification of amaryllis alkaloids were carried out. New chemical procedures, as well as established diagnostic methods, were applied to selected pure alkaloids as part of the structural study.

Major Findings:

A number of new alkaloids occurring in the Amaryllidaceae were characterized. Physicochemical studies provided information on several structural relationships of importance in this group of compounds. A manganese dioxide oxidation method was studied in detail and was applied successfully in structural studies on lycorenine. New degradation products of tazettine were obtained.

Significance to Heart Research:

The structure of most of these alkaloids is unknown and it is expected that new information about naturally occurring polycyclic amines will result from this work. The physiological activity of these alkaloids is under study and one was found to have a distinct hypotensive action.

Proposed course of study:

Much of next year will be spent on structural studies of tazettine and other selected alkaloids of this group. Very little new isolation work will be undertaken; most of the major sources of Amaryllidaceae alkaloids were examined last year.

The degradation work will be accompanied by and correlated with synthetic studies on hydrophenanthridines and related compounds.

R. P. C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 122

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	38,600	4	2	6	3.50	2.00	5.50	
FY 1956	38,600	4	2	6	3.50	2.00	5.50	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None.

14. None.

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-122
SERIAL NO.

16. PUBLICATIONS:

The Isolation of Tazettine and Lycorine from certain Hymenocallis Spp. By W. C. Wildman and C. J. Kaufman, J. Am. Chem. Soc., 76, 5815 (1954).

The Identity of Lycoremine and Galanthamine. By W. C. Wildman, Chemistry and Industry, 1954, 1453.

In Press

Alkaloids of the Amaryllidaceae III. Isolation of Five New Alkaloids from Haemanthus Spp. By C. J. Kaufman and W. C. Wildman, J. Am. Chem. Soc., (1955).

Alkaloids of the Amaryllidaceae IV. Crystalline Alkaloids of Amocharis coranica (Ker-Gawl) Herb., Brunsvigia rosea (Lam.) Hannibal, and Two Crinum Spp. By L. H. Mason, E. R. Puschett and W. C. Wildman, J. Am. Chem. Soc., (1955).

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO. NHI - 123
6. PROJECT TITLE: Studies on Andromedotoxin
7. PRINCIPAL INVESTIGATORS: Mr. W. H. Tallent
8. OTHER INVESTIGATORS: Dr. V. L. Stromberg
9. PROJECT DESCRIPTION:

Objective:

A number of plants related to Rhododendron maximum are being investigated as possible points of occurrence of andromedotoxin. The current process for the purification of andromedotoxin is also under study, and chemical degradation work directed to determining the structure of andromedotoxin is under way.

Methods employed:

New techniques for the study of andromedotoxin were developed. These included paper chromatographic and electrophoresis methods. The present course of structural work is concerned with oxidative degradation of the molecule.

Major findings:

Work on andromedotoxin has been hampered by a lack of methods for the separation and identification of this substance and of its degradation products. A promising technique involving paper electrophoresis has been developed and is currently being applied in studies of the occurrence of andromedotoxin in plants other than R. maximum. Structural work has been carried through the first phases and it is now concerned with oxidative degradation work. The structure of this potent hypotensive agent is still unknown.

Significance to Heart Research:

A quantity of andromedotoxin sufficient for pharmacological and clinical studies was isolated and purified. This material was found to be a hypotensive agent whose effect involved activation of the cardiac sinus pressor reflex. It is currently being studied clinically.

Proposed course of project:

Studies on the natural occurrence of this substance will be continued. The course of the chemical degradation studies will depend upon the results obtained from oxidation experiments.

THE UNIVERSITY OF CHICAGO

1920

DEPARTMENT OF CHEMISTRY

LABORATORY OF PHYSICAL CHEMISTRY

CHICAGO, ILL.

1920

REPORT ON THE PROGRESS OF THE WORK IN THE LABORATORY OF PHYSICAL CHEMISTRY DURING THE YEAR 1920

BY

ROBERT H. SPENCER

ASSISTANT PROFESSOR OF CHEMISTRY

CHICAGO, ILL.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 123

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$17,400	3	1	4	1.50	1.00	2.50	
FY 1956	17,400	3	1	4	1.50	1.00	2.50	

12. BUDGET ACTIVITY:

- RESEARCH
- ADMINISTRATION
- REVIEW & APPROVAL
- TECHNICAL ASSISTANCE

13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 123

16. PUBLICATIONS:

Andromedotoxin, A Potent Hypotensive Agent from Rhododendron
maximum. By H. B. Wood, V. L. Stromberg, J. C. Keresztesy, and E.
C. Horning, J. Am. Chem. Soc., 76, 5689 (1954)

17. None

THE UNIVERSITY OF CHICAGO
DIVISION OF THE PHYSICAL SCIENCES

PHYSICS DEPARTMENT

CHICAGO, ILL.

RECEIVED
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R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO : NHI _ 124
6. PROJECT TITLE: Instrumental Studies of Organic Compounds
7. PRINCIPAL INVESTIGATORS: Mrs. I. J. Siewers
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective:

To carry out instrumental studies, particularly those involving infrared and ultraviolet spectroscopy, on organic compounds under study in NHI. This unit also carries out development research on new instrumental techniques connected with research projects of the Laboratory of Chemistry of Natural Products.

Methods employed:

Instrumental procedures of various kinds were employed. Most of them involved applications of spectrophotometric methods.

Major findings:

Many of the results coming from this unit were incorporated into the individual research projects of this Laboratory. One of the useful procedures developed as part of another project was a means of classification of double bond types through infrared spectroscopy.

Significance to Heart Research;

Instrumental studies are important in supporting chemical research work both along synthetic and structure proof lines. This essential contribution usually takes the form of assistance given on individual projects of this Laboratory.

Proposed Course of Study:

This supporting function will be continued, and additional time will be spent on the perfection of new methods for identification or structure proof work.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO: NHI - 124

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$13,500	1	1	2	1	1	2	
FY 1956	\$13,500	1	1	2	1	1	2	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

R. P. C. - 3
December 1954

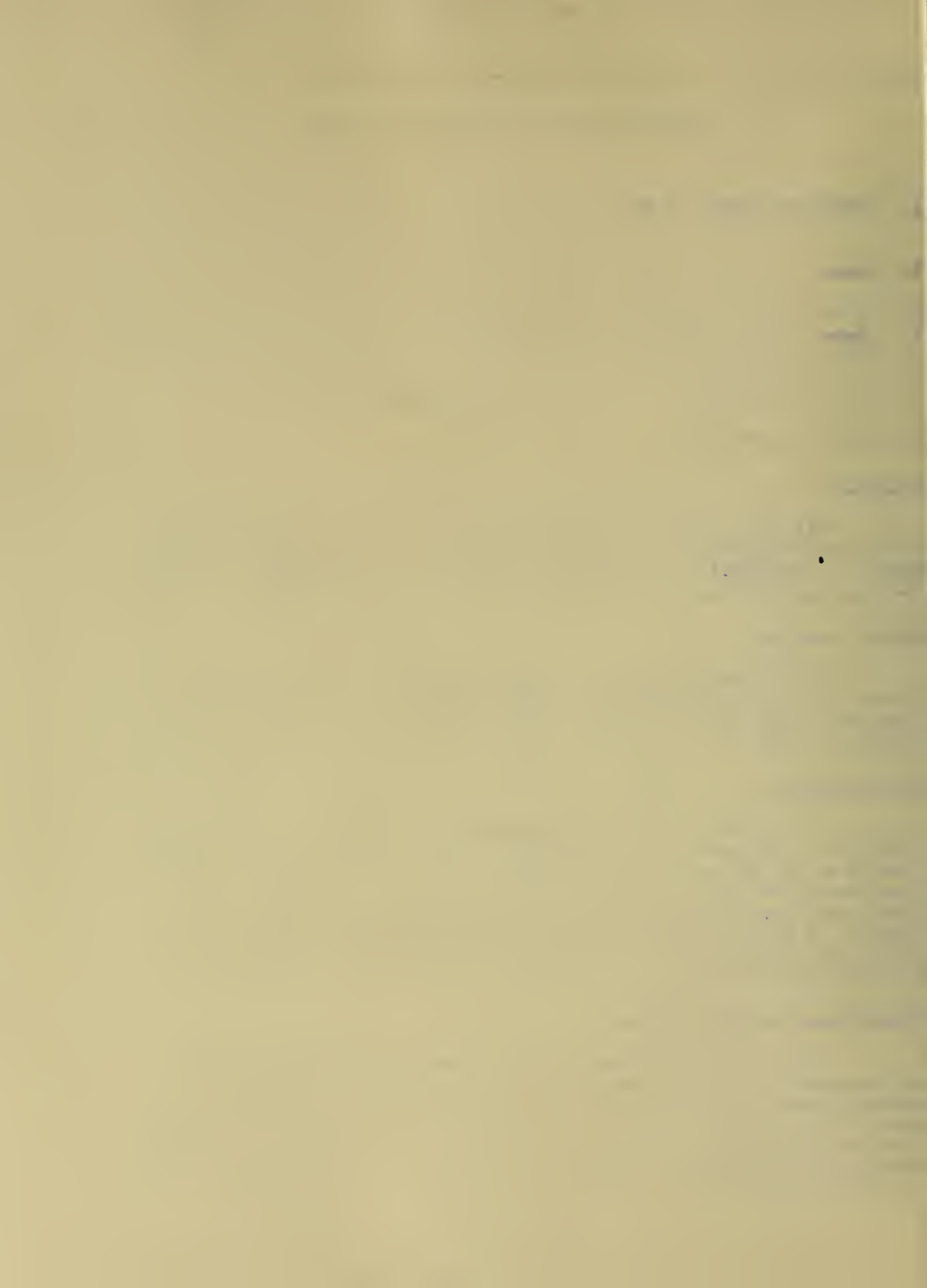
Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 124

16. None

17. None



Project Description Sheet

1. INSTITUTE: National Heart Institute
2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO.: NHI - 125
6. PROJECT TITLE: Studies on Piptadenia spp.
7. PRINCIPAL INVESTIGATORS: Dr. M. S. Fish
8. OTHER INVESTIGATORS: Dr. V. L. Stromberg
9. PROJECT DESCRIPTION:

Objective :

This work is concerned with the isolation, characterization, and structure proof studies of components of Piptadenia peregrina and related species. Substances for study were supplied to the Laboratory of Chemical Pharmacology (NMI) and the Clinical Investigations Branch (NIMH).

Methods employed:

Isolation methods were developed for several basic substances present in Piptadenia peregrina and related species. Chemical investigations of the structure of these compounds indicated that they were rather closely related. Degradation and synthetic studies are in progress.

Major findings:

The principal alkaloid of Piptadenia peregrina was identified as bufotenine. The seeds of this plant were used by Indians of the Caribbean area in major ceremonies, and old reports indicate that reversible mental disturbances resulted from the use of this material. Cooperative work with other units in NIH and NIMH is in progress, but it is not yet possible to tell whether bufotenine is the most active agent in this plant. An important point is the fact that bufotenine may also occur as a component of normal human metabolism.

Significance to Heart Research:

The tranquilizers now in use as hypotensive agents (Rauwolfia or Reserpine, and Chlorpromazine) have an influence on the central nervous system which occurs through an unknown mechanism. Although they cannot be used as drugs, serotonin and bufotenine also affect the central nervous system, and the patterns of effects are apparently related. The fundamental physiological phenomena are unknown, but are of great importance to both heart and central nervous system studies.

R. P. C. - 1
December 1954

Project Description Sheet NHI - 125

Proposed Course of Work:

Work on the isolation of components from Piptadenia spp. will continue. This will be accompanied by tissue isolation studies. Structure proof work will continue on the unknown materials.



R. P. C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO. : NHI - 125

11. BUDGET DATA:

	Estimated Expenditures	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$9,600	2	1	3	1.00	.50	1.50	
FY 1956	13,300	3	1	4	1.50	.50	2.00	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 125

16. PUBLICATIONS:

"The Isolation of Bufotenine and Piptadenia peregrina". By
V. L. Stromberg, J. Am. Chem. Soc., 76, 1707 (1954).

17. None.

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of Natural Products
5. SERIAL NO.: NHI - 126
6. PROJECT TITLE: Synthesis of Oxindoles, Indoles, and Related Polycyclic Systems.
7. PRINCIPAL INVESTIGATORS: Dr. G. N. Walker
8. OTHER INVESTIGATORS: None
9. PROJECT DESCRIPTION:

Objective

To pursue the fundamental chemistry of these substances with a view to developing new synthetic methods.

Methods:

A variety of synthetic chemical techniques and procedures were studied. The structures of the products were determined by chemical and instrumental means.

Major findings:

A reductive cyclization method was developed for the synthesis of 5,6 - dimethoxyoxindoles and indoles. Several methoxyisoquinolines were found to have hypotensive properties.

Significance to Heart Research:

Both simple and polycyclic indoles and related compounds are important in metabolism and in tranquilizing effects. These studies have provided new means of preparing compounds in this general area. The isoquinolines which were investigated were found to have moderate hypotensive properties.

Proposed course of work:

Studies on the synthesis of polycyclic amines will be continued.

R. P. C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO: NHI - 126

11. BUDGET DATA:

	<u>Estimated</u> <u>Expenditures</u>	<u>POSITIONS</u>			<u>MAN YEARS</u>			<u>PATIENT</u> <u>DAYS</u>
		<u>PROF</u>	<u>OTHER</u>	<u>TOTAL</u>	<u>PROF</u>	<u>OTHER</u>	<u>TOTAL</u>	
FY 1955	7,700	1	0	1	1	0	1	
FY 1956	7,700	1	0	1	1	0	1	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 126

16. PUBLICATIONS:

"Hypotensive Methoxyisoquinolines". By G. N. Walker
J. Am. Chem. Soc., 76, 3999 (1954).

"Identify of Some 1- (3,4 - Dimethoxyphenyl) -
6,7-dimethoxytetrolin Derivatives". By R. D. Haworth and G. N. Walker,
J. Am. Chem. Soc., 76, 3496 (1954).

In Press:

"Synthesis of 5,6 - Dimethoxyoxindoles and Oxindoles". By
G. N. Walker, J. Am. Chem. Soc., 77 (1955).

"Stobbe Condensation of 3,4,5-Trimethoxybenzaldehyde and Ethyl
Homopiperonylsuccinate." By G. N. Walker, J. Am. Chem. Soc., 77 (1955).

17. None

R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute 2. LABORATORY: Chemistry of
Natural Products
5. SERIAL NO.: NHI - 127
6. PROJECT TITLE: Discovery of Compounds for the Treatment of Hypertension
7. PRINCIPAL INVESTIGATORS: 4 Positions, new in 1956
8. OTHER INVESTIGATORS: 5 Positions, new in 1956
9. PROJECT DESCRIPTION:

Additional funds acquired in FY 1956 will be utilized to accelerate isolation, structure proof, and synthetic studies of compounds in order to provide more extensive clinical research in the treatment of hypertension.

Analysis of NIH Program Activities

Budget Data Sheet

10. SERIAL NO.: NHI - 127

11. BUDGET DATA:

	Estimated	POSITIONS			MAN YEARS			PATIENT DAYS
	Expenditures	PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	0	0	0	0	0	0	0	
FY 1956	\$52,000	4	5	9	4	5	9	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. None

14. None

R. P. C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. SERIAL NO.: NHI - 127

16. None

17. None

Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Mechanism of Drug Metabolism
PROJECT TITLE

5. NHI-128
SERIAL NO.

B. B. Brodie, James Gillette, B. La Du, C. Mitoma, P. Peyser, S. Udenfriend
PRINCIPAL INVESTIGATORS

PROJECT DESCRIPTION:

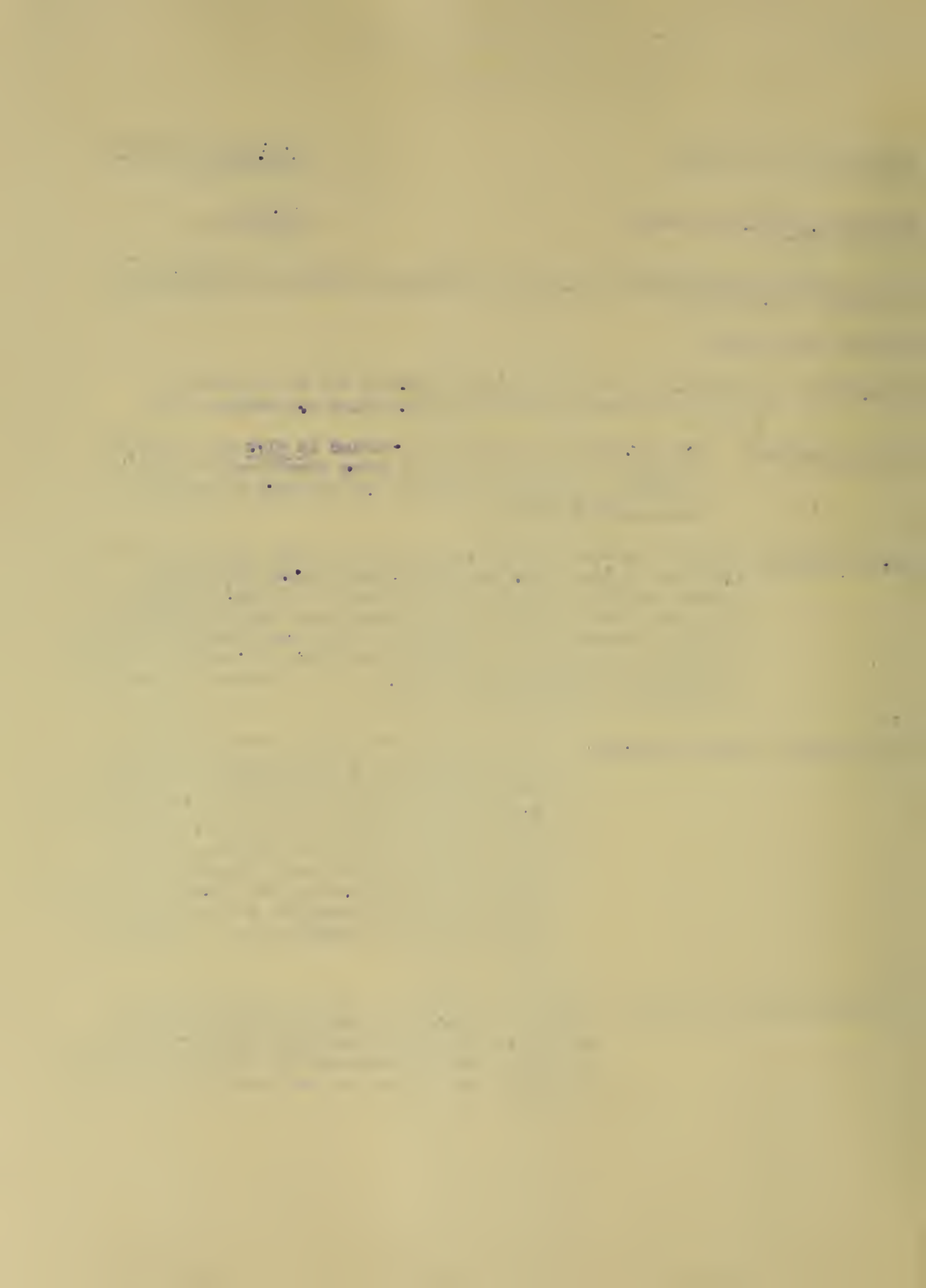
Objectives: To establish how various types of drugs are metabolized in the body and whether specific detoxication mechanisms exist.

Methods Employed: Drug metabolism pathways are studied in vivo and in vitro and enzyme systems catalyzing these reactions are studied in detail. Metabolic products are measured by specific microchemical methods.

Major Findings: Enzyme systems catalyzing most types of drug metabolism are located in liver microsomes (sub-microscopic particles). These reactions include dealkylation of alkylamines, oxidation of barbiturate side chains, desamination of sympathomimetic amines, hydroxylation of aromatic rings, and cleavage of ethers. These systems also have similar requirements; reduced triphosphopyridine nucleotide and oxygen and are blocked by the same inhibitors SKF 525-A etc.

Significance to Heart Research: Most drugs are extensively metabolized in the body and their pharmacological effectiveness depends in part on how effectively these detoxication mechanisms operate. Understanding these mechanisms may be helpful in developing new drugs of longer or shorter duration. Since the detoxication mechanisms vary in different animal species, the observed differences in toxicity and response to drugs in different species may now be explained on a biochemical level.

Proposed course of project: During the coming year several problems to be investigated are: (1) how many types of drug metabolism are present in liver microsomes, (2) are there special mechanisms for drugs and foreign compounds, and (3) how do they operate (mechanism).



Analysis of NIH Program Activities

Budget Data Sheet

1. NHL-128
SERIAL NO.

2. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS		TOTAL	MAN YEARS		TOTAL DAYS
		PROF	OTHER		PROF	OTHER	
FY 1955	\$13,800	7	5	12	3.00	3.67	-
FY 1956	\$13,800	7	5	12	3.00	3.67	-

3. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL

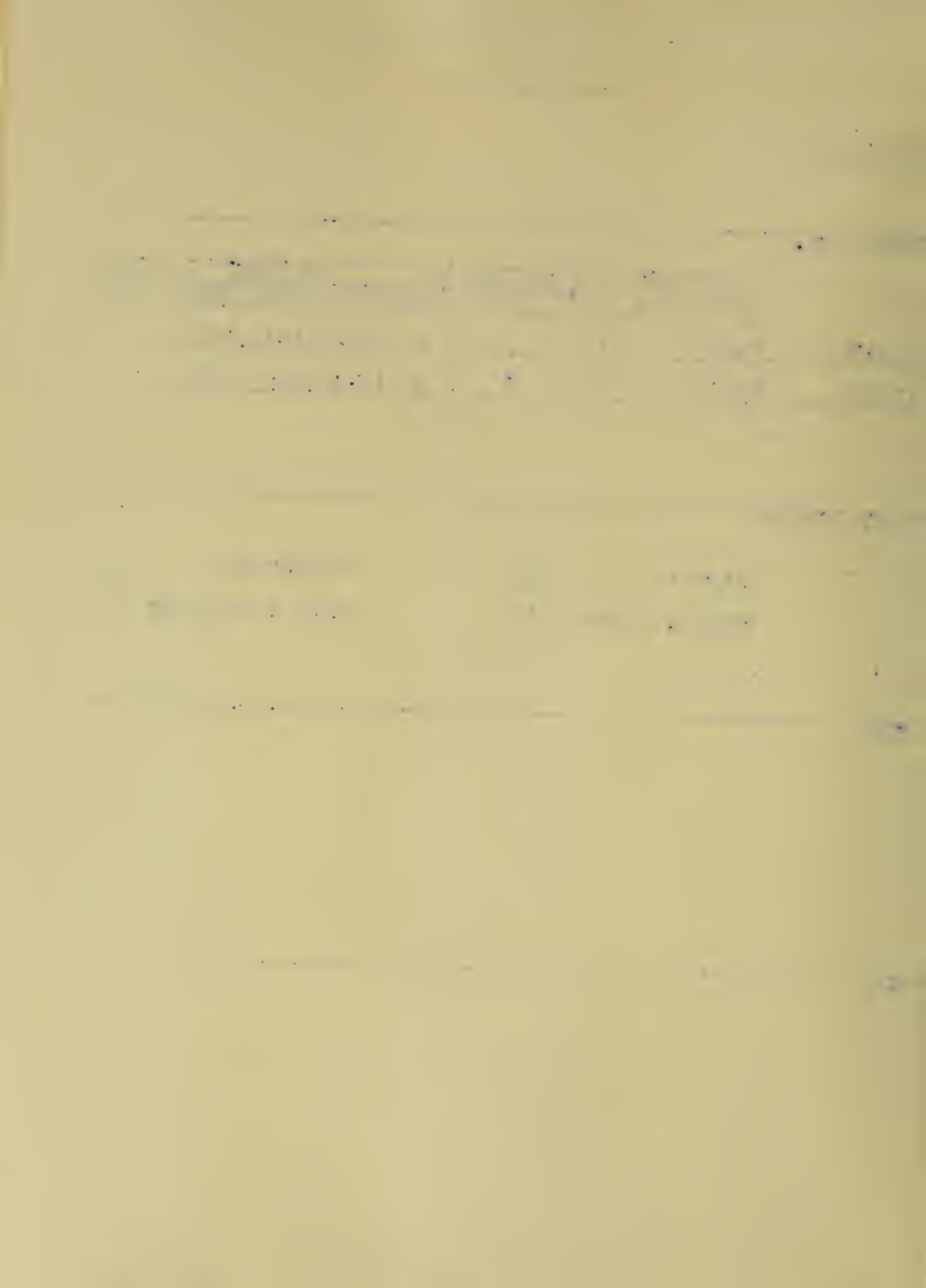


TECHNICAL ASSISTANCE



4. None

5. None



Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NIH-128

SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

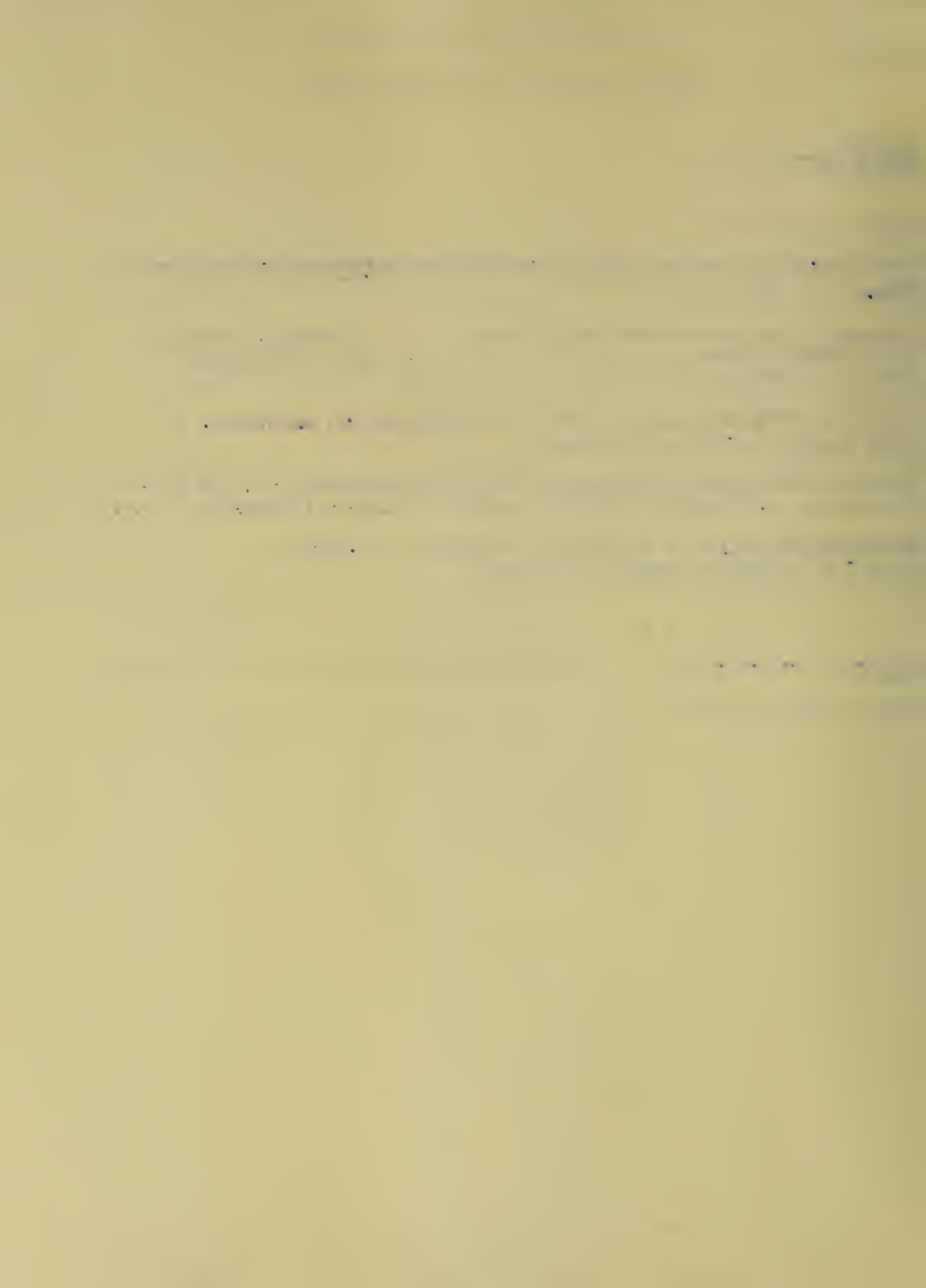
Biochemical Defenses Against Foreign Compounds, B. B. Brodie, J. Axelrod, J. R. Cooper, L. Gaudette, B. N. La Du, C. Mitoma, and S. Udenfriend, Science (in press).

Conversion of Phenylalanine to Tyrosine, Udenfriend, S., and Mitoma, C., Johns Hopkins Univ. Press (in press).

Enzymatic Dealkylation of Aminopyrine and Other Alkylamines, B. N. La Du, Jr., L. Gaudette, N. Trousof, B. Brodie. Journal of Biological Chemistry (in press).

Enzymatic Deamination of Amphetamine (Dexadrine), J. Axelrod
Journal of Biological Chemistry (in press).

None



Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Studies on the Blood-Brain Barrier
PROJECT TITLE

5. NHI-129
SERIAL NO.

Steven Mayer, Bernard B. Brodie
PRINCIPAL INVESTIGATORS

PROJECT DESCRIPTION:

Objectives: To study the locus of the blood-brain barrier and the mechanism whereby drugs pass into the central nervous system.

Methods Employed: Micro methods for the determination of drugs will be used, as well as surgical procedures for the sampling of various parts of the central nervous system.

Major Findings: This project is just getting under way.

Significance to Heart Research: Many drugs used in cardiovascular diseases act through the central nervous system but little is known about the structural requirements for drugs to pass the blood-brain barrier.

Proposed course of project: Drugs will be given intravenously and samples of cerebrospinal fluid, cerebral cortex, and venous blood will be taken. From results obtained it will be possible to make quantitative determination of dynamics and sites of entrance of the various drugs acting on the central nervous system.

Analysis of NIH Program Activities

Budget Data Sheet

NHI-129
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$12,900	2	1	3	.83	.34	1.17	-
FY 1956	\$16,000	2	2	4	.83	1.34	2.17	

BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

None

None

C. - 3
mber 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHI-129
SERIAL NO.

None

None

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Chemical
Pharmacology

PROJECT TITLE: Studies on Anti-rheumatic Drugs

5. SERIAL NO.: NHI-130

PRINCIPAL INVESTIGATORS: B. Burns
B. Brodie

PROJECT DESCRIPTION:

Objectives: Screening of non-steroidal, anti-inflammatory agents in man.

Methods Employed: Micro methods for drug analysis, micro isolation techniques for isolation of metabolites, clinical evaluation of the anti-rheumatic effects of various drugs.

Major Findings: (a) In collaboration with Geigy Pharmaceuticals, a drug, G-25671, has been developed which has considerable anti-rheumatic effects, uricosuric action, and does not cause sodium and water retention. This drug is now on trial in several laboratories in the treatment of chronic gout.

(b) Two metabolites of butazolidin have been isolated and identified. Both compounds exert considerable physiologic effects and it is possible that a considerable amount of the toxicity and/or activity of butazolidin may be exerted through the metabolites.

Significance to Heart Research: A suitable non-steroidal anti-rheumatic agent would be of value not only in the treatment of rheumatoid arthritis, gout, etc., but also in the treatment of rheumatic fever.

Proposed course of project: The screening of non-steroidal anti-rheumatic agents in man will be continued as well as studies on the metabolites of butazolidin.

Analysis of HIS Program Activities

Budget Data Sheet

NHI-130
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	\$2,600	2	0	2	.50	-	.50	-
FY 1956	\$2,600	2	0	2	.50	-	.50	-

BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

This is in collaboration with New York University Research Service (Goldwater Memorial Hospital), Geigy Pharmaceuticals, and Hoffmann-La Roche.

None

Analysis of NIH Program Activities

~~NHI-130~~
SERIAL NO.

Honors, Awards and Publications Sheet

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR
1954:

Effect of Phenylbutazone (Butazolidin) on Experimentally Induced Ocular
Inflammation. Norman Yourish, Bruce Paton, J. J. Burns, and Bernard B. Brodie.
Arch. of Ophth. (in press).

Observations on the Metabolic Transformation and Effects of Phenylbutazone in
Subjects with Hepatic Disease. Murray Weiner, Theodore Chenkin, and J. J. Burns.
Am. J. of the Med. Sci. 228: 36, 1954.

Observations on G-25671, a Phenylbutazone Analogue (4-(phenylthioethyl)-1,2-
diphenyl 3,5-pyrazolidinedione). Bernard B. Brodie, T. F. Yu, J. J. Burns,
Theodore Chenkin, Bruce C. Paton, J. Murray Steele and Alexander B. Gutman.
Proc. Soc. for Exp. Biol. and Med. 86: 884, 1954.

None

Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Patterns of Drug Distribution
PROJECT TITLE

5. NHI-131
SERIAL NO.

G. Tomkins, Steven Mayer, Norman Salzman, B. Brodie
PRINCIPAL INVESTIGATORS

PROJECT DESCRIPTION:

Objectives: The objective of this project is to study the mechanism whereby drugs are localized in body tissues and the effect of tissue localization on drug action.

Methods Employed: Micro methods for the estimation of various drugs and differential centrifugation for the separation of cellular components.

Major Findings: (a) The mechanism whereby butazolidin reaches a limiting concentration no matter how high the dosage has been elucidated.

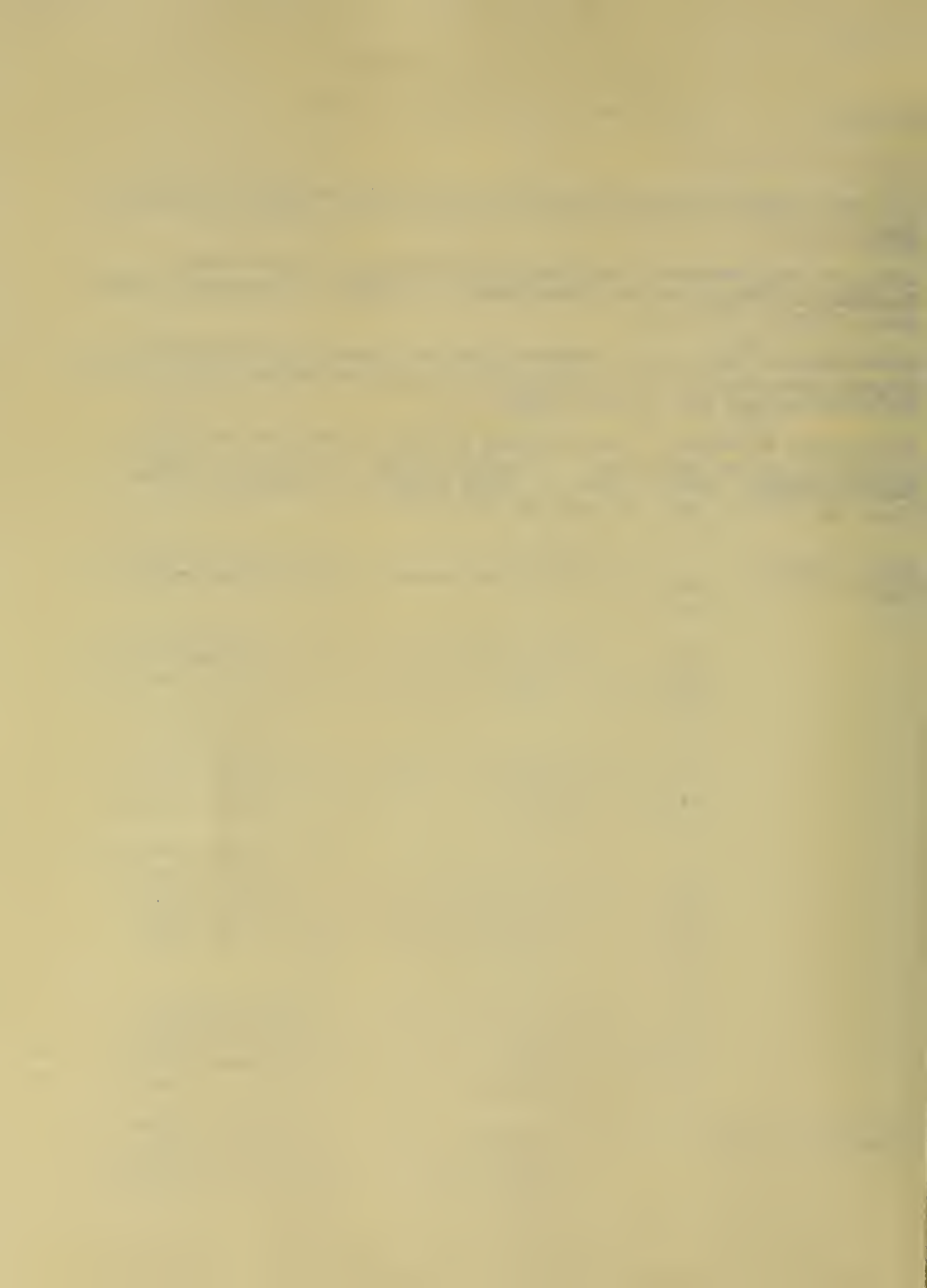
This mechanism is tied up with the avid localization of drug on only a few binding sites which approach saturation at therapeutic plasma levels. The excess unbound drug is then rapidly metabolized.

(b) The acridines, including atabrine, are extensively concentrated in various tissues because of their almost complete localization in various cell nuclei. The physico-chemical properties of this binding have been worked out.

(c) Certain acridones which are central nervous convulsants have a preferential affinity for the nuclei of brain cells. High concentrations found at first in the brain decline rapidly as the nuclei of other tissues take up the drug. This redistribution phenomenon accounts for the short duration of action of these convulsants.

(d) There is no blood brain barrier to entrance of thiobarbiturate into brain and the limiting factor controlling its passage into the central nervous system is the rate of blood flow. The rapidity of passage of barbiturates into brain is related to their fat solubility.

Significance to Heart Research: Knowledge of the basic physiological disposition of cardiovascular drugs leads to their more rational use, defines their limitations, and suggests the synthesis of better drugs.



Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Patterns of Drug Distribution
PROJECT TITLE

5. NHI-131
SERIAL NO.

G. Tomkins, Steven Mayer, Norman Salzman, B. Brodie
PRINCIPAL INVESTIGATORS

PROJECT DESCRIPTION:

Objectives: The objective of this project is to study the mechanism whereby drugs are localized in body tissues and the effect of tissue localization on drug action.

Methods Employed: Micro methods for the estimation of various drugs and differential centrifugation for the separation of cellular components.

Major Findings: (a) The mechanism whereby butazolidin reaches a limiting concentration no matter how high the dosage has been elucidated.

This mechanism is tied up with the avid localization of drug on only a few binding sites which approach saturation at therapeutic plasma levels. The excess unbound drug is then rapidly metabolized.

(b) The acridines, including atabrine, are extensively concentrated in various tissues because of their almost complete localization in various cell nuclei. The physico-chemical properties of this binding have been worked out.

(c) Certain acridones which are central nervous convulsants have a preferential affinity for the nuclei of brain cells. High concentrations found at first in the brain decline rapidly as the nuclei of other tissues take up the drug. This redistribution phenomenon accounts for the short duration of action of these convulsants.

(d) There is no blood brain barrier to entrance of thiobarbiturate into brain and the limiting factor controlling its passage into the central nervous system is the rate of blood flow. The rapidity of passage of barbiturates into brain is related to their fat solubility.

Significance to Heart Research: Knowledge of the basic physiological disposition of cardiovascular drugs leads to their more rational use, defines their limitations, and suggests the synthesis of better drugs.

Proposed course of project: Work in the coming year will be devoted to further studies on the various mechanisms whereby the body localizes drugs. This will include studies on protein binding, nuclei binding, etc.

NHI-131
SERIAL NO.

Budget Data Sheet

NHI-131
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$23,100	4	2	6	2.00	1.50	3.50	-
FY 1956	\$25,100	4	2	6	2.00	1.50	3.50	-

BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

None

None

P.C. - 4
ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHI-131
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Localization of Atebrine and other Acridines in Cell Nuclei, G. Tomkins, R. J. Weiss, and Bernard B. Brodie. (in preparation).

Physiological Disposition of Certain N-Alkyl Thiobarbiturates. E. M. Papper, R. G. Peterson, J. J. Burns, E. Bernstein, P. Lief, and B. B. Brodie. Anesthesiology. In press.

Dorsal Root Ganglion Blockade During Threshold Segmental Spinal Anesthesia in Man. M. Jack Frumin, Herman Schwartz, J. J. Burns, Bernard B. Brodie, and E. M. Papper. J. Pharm. and Exp. Therap. 112, 387, 1954.

None

P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. INSTITUTE: National Heart Institute

2. LABORATORY: Chemical
Pharmacology

PROJECT TITLE: Secretion and Absorption of
Drugs from Stomach and Intestine

5. SERIAL NO.: NHI-132

PRINCIPAL INVESTIGATORS: Parkhurst A. Shore (in collaboration with Dr. Adrien
B. Brodie Hogben, K&E)

PROJECT DESCRIPTION:

Objectives: To study the mechanism of the secretion and absorption of drugs
by the digestive tract.

Methods Employed: Heidenhain pouches are used in dogs for the study of gastric
absorption. Rats with gastrointestinal tract cannulated at
both ends are used for the study of absorption from the gut.

Major Findings: Basic drugs when given parenterally are secreted into the
gastric juice in high concentration. The mechanism of this
secretion has been elucidated.

Acidic drugs when given orally may be absorbed directly from
the stomach to a considerable degree. Basic drugs are
usually not absorbed directly from the stomach.

Significance to HEART Research: A number of cardiovascular drugs would be
very useful if they were absorbed well when
given orally. More information is needed
concerning the mechanism of absorption in
order to guide the chemist in the synthesis
of more suitable agents.

Proposed course of project: During the next year studies will be pursued on
the mechanism of absorption of drugs from the gut.

Analysis of NIH Program Activities

Budget Data Sheet

10. 1-1-132
SMITH, C.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			FISCAL YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	15,100	2	1	3	.67	.33	1.00	
FY 1956	15,500	2	1	3	.67	.33	1.00	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13.

14.

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December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NIH-132
SERIAL NO.

16. NONE

17. NONE

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Chemical
Pharmacology

PROJECT TITLE: Mechanism of Drug Potentiation

5. SERIAL NO.: NHI-133

PRINCIPAL INVESTIGATORS: J. Fouts
P. Shore
B. Brodie

PROJECT DESCRIPTION:

Objectives: To find out how certain compounds markedly potentiate the action of drugs.

Methods Employed: Micro methods of analysis of drugs.

Major Findings: (a) A number of derivatives of diphenylpropylacetic acid (SKF 525-A) prolong the action of the majority of drugs by inhibiting their rate of biotransformation. This observation has led to the finding that the majority of enzymes involved in the metabolism of drugs have certain common denominators, including localization in liver microsomes and a requirement for both TPNH and oxygen.

(b) Two other chemical series - derivatives of phenylphenoxy-ethyl diethylamine (Lilly 18947) and the anti-TB compound Isoniazid and Marsilid, also inhibit the metabolism of practically all drugs, probably by the same mechanism as does SKF 525-A. The Lilly compound is considerably more active in vivo than SKF 525-A.

(c) Chlorpromazine, which potentiates the action of a number of CNS depressants, does so without altering the rate of metabolism of the drug. Nor does it change the blood-barrier. Thus it acts as a true potentiator rather than as a prolonging agent. A metabolite of chlorpromazine (probably the sulfoxide) has been isolated and has been found not to react as a potentiator.

(d) Reserpine and bufotenin (dimethyl serotonin) have been found to also potentiate central nervous system depressants in a manner similar to chlorpromazine.

Significance to HEART RESEARCH: With the complicated drug combinations now used in cardiovascular disease it is important to realize that one compound may potentiate the action of another. This may be dangerous but may be used to advantage in therapy if known.

Proposed course of project: Other types of potentiation will be studied.

Analysis of NIH Program Activities

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Budget Data Sheet

SERIAL NO.: NHI-133

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	\$20,600	3	1	4	1.33	1.83	3.16	-
FY 1956	\$20,600	3	1	4	1.33	1.83	3.16	-

BUDGET ACTIVITY:

RESEARCH	<input checked="" type="checkbox"/>	ADMINISTRATION	<input type="checkbox"/>
REVIEW & APPROVAL	<input type="checkbox"/>	TECHNICAL ASSISTANCE	<input type="checkbox"/>

None

None

C. - 3
ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHI-133
SERIAL NO.

None

None

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Chemical
Pharmacology

PROJECT TITLE: The Role of Serotonin in the
Action of Reserpine and Chlorpromazine

5. SERIAL NO.: NHI-134

PRINCIPAL INVESTIGATORS: P. Shore
B. Brodie

PROJECT DESCRIPTION:

Objectives: To elucidate the mechanism of action of reserpine and chlorpromazine and to find the role of serotonin in the function of the brain.

Methods Employed: Micro methods of analysis of drugs.

Major Findings: Serotonin, as does reserpine and chlorpromazine has been shown to potentiate the action of CNS depressants. This suggested that reserpine and chlorpromazine might act through liberation or synthesis of serotonin. The diethylamide of lysergic acid (LSD) was shown to block the potentiating effects of serotonin, chlorpromazine, and reserpine. This is the first time that an antagonism between LSD and serotonin has been shown in vivo or the CNS level. The administration of reserpine to dogs results in a marked increase in the excretion of 5-hydroxyindoleacetic acid, the metabolic product of serotonin.

Significance to HEART Research: The mechanism of action of reserpine and chlorpromazine, two compounds important in the treatment of hypertension and mental diseases, has been related to the liberation of the newly discovered hormone, serotonin. These results almost definitely indicate that serotonin plays an important role in the function of the brain.

Proposed course of project: The discovery that reserpine and chlorpromazine probably act through liberation of serotonin will give great impetus to our studies of the role of this new hormone.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIH134
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT
		PRG	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	\$7,700	2	1	3	.67	.50	1.17	-
FY 1956	\$7,700	2	1	3	.67	.50	1.17	-

12. BUDGET ACTIVITY: RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. NONE

14. NONE

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December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. MHI-134
SERIAL No.

16. NONE

17. NONE

Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Cholesterol and Bile Acid Metabolism
PROJECT TITLE

5. NHI-135
SERIAL NO.

Marvin D. Siperstein
PRINCIPAL INVESTIGATOR

PROJECT DESCRIPTION:

Objectives: To study the mechanisms by which the body metabolizes cholesterol and bile acids.

Methods Employed: Through the use of cholesterol labeled in the carbon 4 position, the major pathway of cholesterol degradation and elimination in human beings is being examined. Following the administration of the cholesterol, expired air, urine, feces, and bile are collected and assayed for C^{14} content. The specimens are then subjected to chemical analysis to determine into what compounds cholesterol is converted before excretion.

In addition to the above approach, use is being made of enzymological techniques to study the detailed biochemical steps involved in bile acid metabolism. Cells are being broken and separated by differential centrifugation into their separate components. These are then being examined to determine what role they play in bile acid metabolism.

Primarily this year we have been concerned with studying the mechanism of conjugation of bile acids with amino acids.

Major Findings:

(1) In man cholesterol is excreted primarily (90%) by way of the biliary tract.

(2) During the metabolism of cholesterol only the last three carbons of its isooxyl side chain are removed, and a bile acid is produced as the major metabolic end-product.

(3) In man the bile acid, cholic acid, is the chief biliary metabolite of cholesterol.

(4) Urine and expired air are of little or no importance as routes of elimination for these C^{14} containing end-products.

(5) In studies on the conjugation of cholic acid with the amino acid, taurine, it has been found that this process takes place in the microsomes of the cell and that it requires the presence of adenosine triphosphate, diphosphopyridine nucleotide, coenzyme A, nicotinamide and glucose 6 phosphate.

MEMORANDUM FOR THE DIRECTOR

DATE: 10/25/54

SUBJECT: [Illegible]

RE: [Illegible]

1. [Illegible]

2. [Illegible]

3. [Illegible]

4. [Illegible]

5. [Illegible]

6. [Illegible]

7. [Illegible]

8. [Illegible]

9. [Illegible]

10. [Illegible]

11. [Illegible]

12. [Illegible]

13. [Illegible]

14. [Illegible]

Significance to Heart Research: The deposition of cholesterol in the arterial wall is probably the chief cause of atherosclerosis and heart disease. It is hoped therefore that a knowledge of the metabolism of this sterol will provide a better basis on which to design methods of treatment and prevention of these conditions.

Proposed course of project: Much is yet to be learned about the intimate details of bile acid metabolism and it is planned to pursue this study along the same lines as noted above.

NHI-135
SERIAL NO.

Budget Data Sheet

NHI-135
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	\$5,100	1	1	2	.50	.50	1.00	-
FY 1956	\$5,100	1	1	2	.50	.50	1.00	-

BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



Nons

Nons

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ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHL-135
SERIAL NO.

None

None

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY OR BRANCH

5. NHI-136
SERIAL No.

6. The effects of Hypothermia and Anesthesia on Respiratory and Circulatory
PROJECT TITLE Physiology

7. John W. Soveringhaus and Maurice Stumpf
PRINCIPAL INVESTIGATOR(S)

9. PROJECT DESCRIPTION

Objectives: To determine the effect of body hypothermia, various types of anaesthesia, techniques, position, pressure respiration, the open chest and shock on the following respiratory variables: (1) Anatomic dead space; (2) physiologic dead space; (3) alveolar dead space; (4) effective shunts or venous admixture; (5) bronchial tone; (6) lung mechanics.

To determine the effect of hypothermia on myocardial blood flow distribution by radio-autographic or staining techniques.

Methods Employed: apparatus includes oxygen and CO₂ analyzers for gas and blood-gas, pH meter, thermocouple recorder, pressure indicators and recorders. The dogs are ventilated artificially and samples of blood and gas are taken simultaneously under various conditions.

Major Findings: All dead spaces increase and shunts decrease during hypothermia. No results reportable to date on myocardial blood flow distribution.

Significance to HEART Research: Heart surgery is expanding and using hypothermia techniques, which need to be more carefully controlled and their effects understood.

Proposed course of project: The next calendar year will be devoted primarily to continued investigation of the above-described program.

Analysis of NIH Program Activities

Budget Data Sheet

10. NEI-136
LABORATORY

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	FY 1955			FY 1956			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,200	---	---	---	---	---	---	
FY 1956	\$5,100	---	---	---	---	---	---	

12. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
 REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Anesthesia Dept., Clinical Center, NIH

14. NIH

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ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHI-136
SERIAL NO.

None

None

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Analysis of NIH Program Activities

Program Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Development of a Spectrophotofluorimeter for Measurement of
Ultraviolet Fluorescence
PROJECT TITLE

5. NHI-137
SERIAL NO.

Sidney Udenfriend
PRINCIPAL INVESTIGATOR

PROJECT DESCRIPTION:

Objectives: To develop an apparatus which can activate and measure emitted fluorescence continuously throughout the ultraviolet and visible range.

Methods Employed: - - -

Major Findings: A laboratory instrument has been developed which can satisfactorily carry out the objectives given above. Studies have been carried out on many compounds of biochemical and pharmacological interest.

Significance to HEART Research: Micro techniques for chemical assay are needed to solve pharmacological and biochemical problems in cardiovascular studies.

Proposed course of project: The American Instrument Company is building an instrument modeled after the one constructed in the Heart Institute. This instrument will be made available to this group for further study and for applications to analytical problems.

Analysis of NIH Program Activities

Budget Data Sheet

NHI-137
 SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		1 PROF	2 OTHER	3 TOTAL	.33 PROF	.67 OTHER	1.00 TOTAL	
FY 1955	\$5,100	1	2	3	.33	.67	1.00	-
FY 1956	\$5,100	1	2	3	.33	.67	1.00	-

BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
 REVIEW & APPROVAL TECHNICAL ASSISTANCE

IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Collaboration with Dr. Robert Bowman, Laboratory of Technical Development

American Instrument Company, Silver Spring, Md., is designing a new instrument and may pay for a post-doctorate fellow to carry on further studies in this laboratory.

None

Particulars		Debit	Credit
By Balance			1000
To Cash		500	
To Bank		500	
Total		1000	1000

- Cash
- Bank
- Debtors
- Creditors

The following is a list of the assets and liabilities of the business as at the end of the year. The total of the assets is equal to the total of the liabilities, which is a check on the accuracy of the accounts.

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHI-137
SERIAL NO.

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Chemical Estimation of Serotonin in Biological Tissues, S. Udenfriend, C. Clark, and H. Weissbach, J. Biol. Chem. (in press).

Ultraviolet activated - Ultraviolet Emission Fluorescence - Application to Serotonin and Other Indoles, R. Bowman, P. Cahlfeld, and S. Udenfriend, Science. (in press).

7. None

Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Studies on Ascorbic Acid
PROJECT TITLE

5. NHI-138
SERIAL NO.

John Burns
PRINCIPAL INVESTIGATOR

PROJECT DESCRIPTION:

Objectives: To investigate the pathway of biosynthesis and metabolism of ascorbic acid and the factors involved in its physiological disposition.

Methods Employed: In vivo administration of radioactive precursors. Administration of drugs which increase ascorbic acid formation.

Major Findings: Radioactive glucose serves as a precursor of ascorbic acid but sorbose does not.

In humans C^{14} ascorbic acid is slowly metabolized compared to guinea pigs. The major end product is oxalic acid as in guinea pigs.

L-ascorbic acid and D-ascorbic acid are handled quite differently in rats. The unnatural D-isomer is not localized and is rapidly excreted in the urine whereas the natural form is localized in tissue and slowly excreted.

The inability of D-ascorbic acid to be retained in the body compared to its L-isomer may explain why it has no anti-scorbutic activity.

Significance to HEART Research: Vitamin C (ascorbic acid) is involved in maintaining the integrity of all tissues and organs including the heart and cardiovascular system.

Proposed course of project: Other precursors of ascorbic acid will be investigated both in vivo and in vitro.

The mechanism involved in the binding of ascorbic acid by tissues will be investigated.

Budget Data Sheet

NHI-138
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$12,900	1	2	3	.50	1.33	1.83	-
FY 1956	\$12,900	1	2	3	.50	1.33	1.83	-

BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



None

IF THIS PROJECT RESSEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Studies on the metabolism of C^{14} ascorbic acid in humans have been carried out in collaboration with Dr. Leon Hellman of the Sloan-Kittering Institute, New York.

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ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHI-138
SERIAL NO.

LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR
1954:

Studies on the Incorporation of C^{14} Administered as L-Sorbose into
L-Ascorbic Acid and D-Glucose in Rats. J. J. Burns, E. H. Mosbach,
Shirley Schulenberg and Jules Reichenthal. J. Biol. Chem. (in press)

None

Budget Data Sheet

10. MHI-139
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$28,300	5	3	8	2.67	1.67	4.34	
FY 1956	\$28,300	5	3	8	2.67	1.67	4.34	

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. NONE

14. NONE

Honors, Awards, and Publications Sheet

15. NHI-139
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING THE CALENDAR YEAR 1954:

Clark, C. T., Weissbach, H., and Udenfriend, S.: 5-Hydroxytryptophan Decarboxylase: Preparation and Properties, *J. Biol. Chem.* 210, 139, 1954.

Udenfriend, S., Clark, C., and Weissbach, H.: The Estimation of 5-Hydroxytryptamine (Serotonin) in Biological Tissues, *J. Biol. Chem.* (in press).

Nitomi, C., Weissbach, H., and Udenfriend, S.: Formation of 5-Hydroxytryptophan from Tryptophan by Chromobacterium violaceum, *J. Am. Chem. Soc.* (in press).

Udenfriend, S., Page, I. H., and Gorcoran, A. C.: Diagnostic Value of Urinary 5-Hydroxyindoleacetic Acid in Malignant Carcinoid, *Lancet* (in press).

17. NONE

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Chemical
Pharmacology

PROJECT TITLE: Biosynthesis of Epinephrine and
Norepinephrine

5. SERIAL NO.: NEI-340

PRINCIPAL INVESTIGATORS: Pinus Peyser
Sidney Udenfriend
Donald Bogdanski

PROJECT DESCRIPTION:

Objectives: To elucidate the mechanism of the biosynthesis of epinephrine and norepinephrine by characterizing the intermediate precursors and the enzyme systems involved.

Methods Employed: Standard isotopic and enzymatic techniques.

Major Findings: Phenylalanine, tyrosine and dihydroxyphenylalanine can serve as precursors of adrenal epinephrine and norepinephrine.

Significance to HEART Research: Provides basic information concerning these two hormonal agents which can profoundly influence the cardiovascular system.

Proposed course of project: Further intermediates in the biogenesis of these agents will be sought. Studies will be continued on the cellular catalysts involved. Studies will be initiated on the rate of formation of adrenal epinephrine in vivo.

Analysis of NJO Program Activities

Budget Data Sheet

10. NHI-140
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			TOTAL DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	12,900	3	2	5	1.17	.67	1.84	-
FY 1956	12,900	3	2	5	1.17	.67	1.84	-

12. BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



13. NONE

14. NONE

R.P.G. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-140
SERIAL NO.

16. NONE

17. NONE

P.C. - 1
ember 1954

Analysis of NIH Program Activities

Project Description Sheet

National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

Studies on the Acute Toxicity of Sodium Fluoride
PROJECT TITLE

5. NHI-141
SERIAL NO.

Dr. Neil C. Moran
PRINCIPAL INVESTIGATOR

PROJECT DESCRIPTION:

Objectives: To describe the acute toxic effects of sodium fluoride in dogs, the lethal dose on i.v. administration, and the pathological changes in the tissues. To provide a guide to safe dose levels for i.v. administration to human subjects for studies on fluoride excretion.

Methods Employed: In unanesthetized dogs measurement of blood pressure, electrocardiograph, respiratory rate, reflexes, blood cytology and serum calcium. Infusion by vein of sodium fluoride to fatal dose in one group and to sub-fatal doses in another group. Sacrifice and autopsy for gross and microscopic examination of tissues.

Major Findings: Acute fatal dose is about 37 mgm/kgm of fluoride ion, producing death by cardiorespiratory failure. Delayed death occurs in 18-36 hours after 20-25 mgm/kgm of fluoride ion due to multiple hemorrhages.

Significance to Heart Research: The clarification of the toxic effects of sodium fluoride on the electrocardiograph, the blood pressure, capillaries will be of value in diagnosis and treatment of fluoride poisoning.

Proposed Course of Project: Continuation of acute studies. Semi-acute (3 week) toxicity studies in dogs with sub-lethal doses.

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Analysis of NIH Program Activities

Budget Data Sheet

0. NHI-141
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$12,900	1	2	3	.50	1.50	2.00	-
FY 1956	\$ 5,000	1	1	2	.50	.50	1.00	-

2. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

3. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

N. I. Dental Research

4. None

P.C. - 3
ember 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

NHI-141
SERIAL NO.

None

None

Analysis of NIH Program Activities

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Chemical Pharmacology

PROJECT TITLE: Studies on Cardiac Drugs

5. SERIAL NO.: NHI-142

PRINCIPAL INVESTIGATORS: Harriet M. Maling
Neil C. Moran

PROJECT DESCRIPTION:

Objectives: I. To screen drugs for antiarrhythmic action. To make detailed studies of antiarrhythmic drugs in terms of physiological disposition, toxicity, duration of action, mechanism of action and other pharmacological actions.

II. To study the action of drugs upon the myocardium and the coronary circulation.

Methods Employed: I. Chloroform-epinephrine ventricular arrhythmias in dogs and cats.

II. The heart-lung preparation of the dog.

Major Findings: Twenty-three out of twenty-eight synthetic antimalarials exhibited antiarrhythmic action in our screening experiments. Sixteen out of seventeen piperidyl-quinolinemethanols tested exhibited antiarrhythmic activity, regardless of the point of attachment of the CHOH-piperidyl side chain to the quinoline nucleus. In particular SN 2157, a quinoline methanol, appeared to have good protective action and a good therapeutic ratio and will be tried in man.

Significance to HEART Research: Possible development of antiarrhythmic drugs for clinical use superior to those now available.

Proposed course of project:

1. Continued screening of drugs.
2. Further detailed studies on SN 2157, a quinoline methanol, which appeared to be worth clinical trial on the basis of screening. Studies to include action in various types of arrhythmias, absorption, physiological disposition, excretion and toxicity. Similar studies on other promising compounds.
3. Cardiac effects of andromedotoxin evaluated on heart-lung preparation. Evaluation of cardiac actions of other drugs including cardiotonic steroid being isolated from liver by Dr. Elwood Titus.

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Analysis of NIH Program Activities
Budget Data Sheet

SERIAL NO.: NHI-142

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	\$15,500	1	2	3	1.00	1.50	2.50	-
FY 1956	\$23,100	2	2	4	1.50	1.50	3.00	-

BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



None

None

P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHL-142
SERIAL NO.

5. None

7. None

Project Description Sheet

INSTITUTE: National Heart Institute

2. LABORATORY: Chemical
Pharmacology

PROJECT TITLE: The Biosynthesis of and the
Isolation of Cardiotonic Substances in
Animals

5. SERIAL NO.: NHI-113

PRINCIPAL INVESTIGATORS: Elwood O. Titus
Marvin D. Siperstein

PROJECT DESCRIPTION:

Objectives: The biosynthesis of and the isolation of cardiotonic substances
in animals.

Methods Employed: Counter-current distribution, paper chromatography,
and staircase technique, using frog heart for the
bioassay of cardiotonic material.

Major Findings: Cardiotonic substances, very similar to digitalis in
both chemical structure and pharmacological effects,
are produced in the venom glands of certain toads.
The mechanism by which these substances are produced
by the toad gland is being investigated with the aid
of isotopically labeled precursors.

Substances with similar digitalis-like activity which
may be structurally similar to the toad products have
been observed in mammalian blood and liver. These are
being isolated for further characterization.

Significance to HEART Research: The normally occurring cardiotonic substance
in mammalian tissue may be a hormone required
for the control of heart action.

Proposed course of project: The physical isolation of the cardiotonic
material will be attempted and the complete
pharmacology of it studied in animals and man.
The biosynthesis of the material will be studied.

Analysis of NIH Program Activities

Budget Data Sheet

10. NIH-113
 Section C.

11. BUDGET DATA:

	ANTICIPATED BUDGET ITEMS	PERSONNEL			MATERIALS			TOTAL
		F&F	OTHER	RETA.	F&F	OTHER	RETA.	
FY 1955	\$15,400	2	2	4	1.50	1.50	2.50	-
FY 1956	\$15,400	2	2	4	1.50	1.50	2.50	-

12. BUDGET ACTIVITY:

RESEARCH

ADMINISTRATION

GENERAL & SPECIAL

ALCOHOL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956; IF COOPERATING UNIT IS WITHIN THE INDICATED BUDGET CODE(S) (ITEM 1)

Laboratory of Kidney and Electrolyte Metabolism,
 Dr. Stephen Bajda - NIH-14

14. NOTE

P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHL-113
SERIAL NO.

6. None

7. None

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Chemical Pharmacology
LABORATORY

3. Enzymatic Reduction of Cortisone and Hydrocortisone
PROJECT TITLE

5. NHI-144
SERIAL NO.

4. G. Tomkins
PRINCIPAL INVESTIGATOR

PROJECT DESCRIPTION:

Objectives: To study the enzyme systems which detoxify cortisone and hydrocortisone.

Methods Employed: The usual techniques of enzyme chemistry.

Major Findings: The No. I ring of cortisone and hydrocortisone and a number of other hormones including testosterone, DOCA and progesterone have an alpha-beta double bond and a ketone group in the first ring of the steroid molecule. These compounds are all reduced by enzyme systems in the soluble fraction of the liver cell. There are two enzyme systems involved, the first reduces the double bond and the second reduces the keto group to an alcohol. Each of the hormones requires a different enzyme system for the first step, while the second step is carried out by a single enzyme system. Either DPNH or TPNH are hydrogen donors in this process.

Significance to HEART Research: Knowledge of the metabolism of hormones is important in an understanding of cardiovascular disease.

Proposed course of project: This project is being discontinued in this laboratory and is being carried on by Dr. G. Tomkins who is transferring to NIAID.

Appendix

The following table shows the results of the survey conducted in the year 2000. The data is presented in a tabular format, with columns representing different categories and rows representing the responses. The table is organized into several sections, each corresponding to a different aspect of the survey. The first section deals with the demographic characteristics of the respondents, including age, gender, and education level. The second section focuses on the respondents' attitudes towards the subject matter being studied. The third section examines the respondents' perceptions of the current situation, and the fourth section discusses their suggestions for improvement. The data is presented in a clear and concise manner, allowing for easy comparison and analysis of the results. The table is organized into several sections, each corresponding to a different aspect of the survey. The first section deals with the demographic characteristics of the respondents, including age, gender, and education level. The second section focuses on the respondents' attitudes towards the subject matter being studied. The third section examines the respondents' perceptions of the current situation, and the fourth section discusses their suggestions for improvement. The data is presented in a clear and concise manner, allowing for easy comparison and analysis of the results.

Budget Data Sheet

NIH-114
SERIAL NO.

BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			TIME DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$5,200	1	1	2	.50	.50	1.00	
FY 1956	00	00	00	00	00	00	00	00

BUDGET ACTIVITY:

RESEARCH



ADMINISTRATION



REVIEW & APPROVAL



TECHNICAL ASSISTANCE



IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNITS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Cooperation with Dr. K. Isselbacher, NIAMD

.P.C. = 3
December 1954

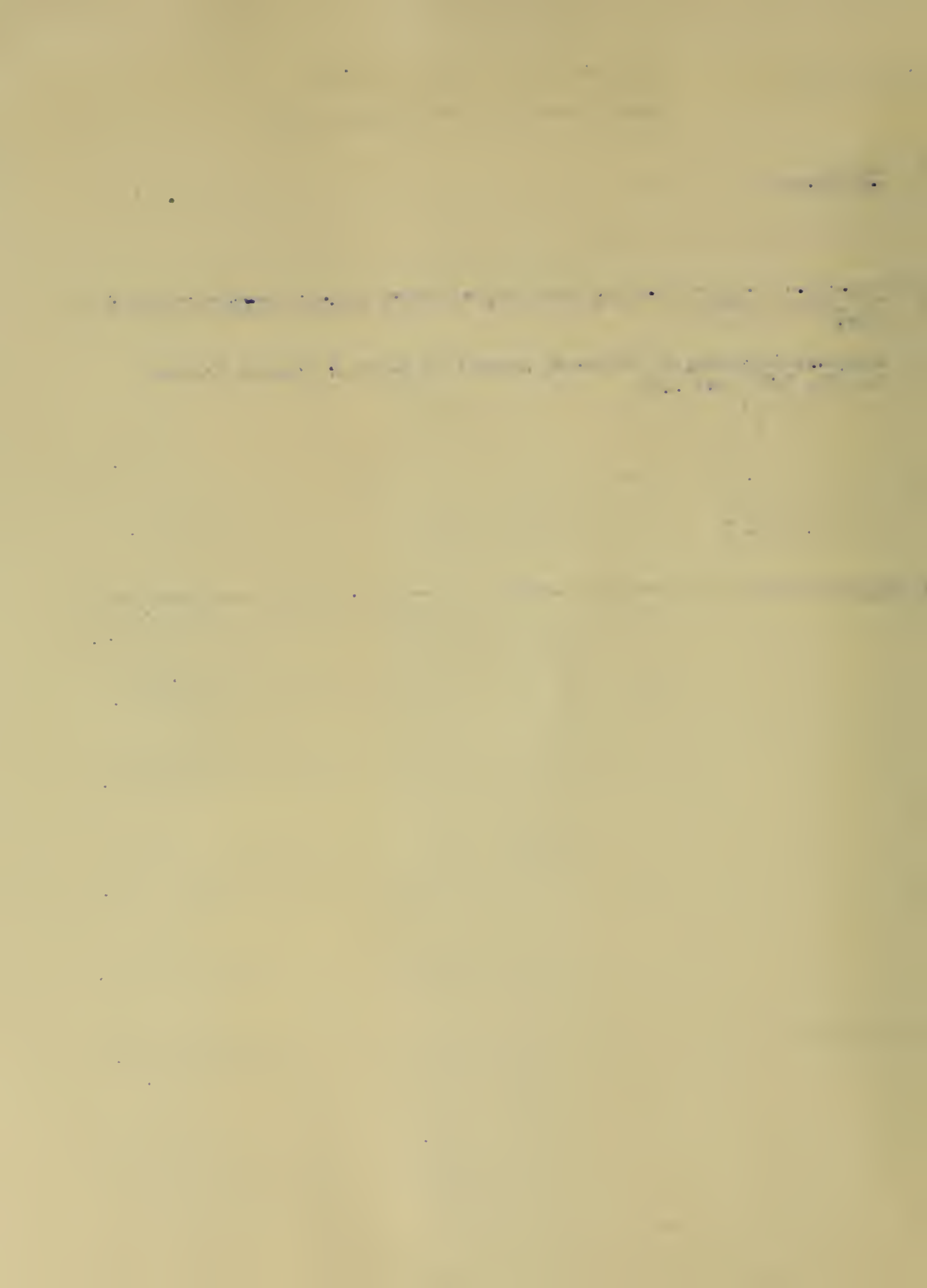
Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

5. NHI-144
SERIAL NO.

6. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR
1954:

Enzymatic Reduction of Cortisone, Journal of American Chemical Society,
Vol. 76, 3100, June 1954.

7. None



Project Description Sheet

- | | |
|---|---|
| 1. <u>National Heart Institute</u>
INSTITUTE | 2. <u>Chemical Pharmacology</u>
LABORATORY |
| 3. <u>Studies on Hypotensive Drugs</u>
PROJECT TITLE | 5. <u>NHI-115</u>
SERIAL NO. |
| 7. <u>Dr. Neil C. Moran</u>
PRINCIPAL INVESTIGATOR | |

9. PROJECT DESCRIPTION

Objectives: 1. To screen new synthetic and plant compounds for hypotensive and other actions. 2. To evaluate mechanism and duration of action and toxicity of active compounds, and 3. to attempt a pharmacological evaluation of mechanisms of vasomotor regulation.

Methods Employed: Standard physiological techniques for recording blood pressure, blood flow, electrocardiograph in animals.

Major Findings:

1. of twenty-five plant and synthetic substances screened two showed striking hypotensive activity. Pilocereine, an alkaloid from a Mexican cactus, although active, develops strong tachyphylaxis and is therefore unsuitable for clinical use. An alkaloid from *Ormosia panamensis* is strongly hypotensive, exhibits no tachyphylaxis and is relatively non-toxic in effective doses.
2. Andromedotoxin, a substance from *Rhododendron maximum*, was found to be poorly absorbed from the gastrointestinal tract.
3. Pilocarpine, a cholinergic drug, has been found to reverse the vasodepressor action of isopropylnorepinephrine, an adrenergic vasodilator drug. Atropine, a cholinergic blocking drug, restores the vasodepressant action of isopropylnorepinephrine.

The significance of this phenomenon in terms of adrenergic vasodilator receptors is under study.

Significance to Heart Research: The discovery of several hypotensive drugs illustrates progress in the search for new, less toxic, longer acting drugs for the treatment of hypertension.

The possible pharmacological characterization of adrenergic vasodilator receptors will add to the knowledge of the role of the autonomic nervous system in vasomotor regulation.

Proposed Course of Project: Continued screening of drugs for possible hypotensive action with studies of mechanism of action of such drugs. Further studies on pilocarpine antagonism of isopropyl norepinephrine to clarify specificity of this phenomenon.

NHT-145
SERIAL NO.

Budget Data Sheet

0. NHL-145
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
FY 1955	\$43,800	7	5	12	3.00	3.67	6.67	-
FY 1956	\$43,800	7	5	12	3.00	3.67	6.67	-

2. BUDGET ACTIVITY:

RESEARCH ADMINISTRATION
REVIEW & APPROVAL TECHNICAL ASSISTANCE

3. None

4. None

R.P.C. - 4
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-145
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

The Action of Andromedotoxin on the Carotid Sinus in Dogs. Neil C. Moran, Marjorie E. Perkins, and Arthur P. Richardson, *Journal of Pharmacology and Experimental Therapeutics*, Vol. III, No. 4, August 1954.

Veratridine Blockade of the Carotid Sinus Pressoreceptors, Neil C. Moran, Marjorie E. Perkins, and Arthur P. Richardson, *Journal of Pharmacology and Experimental Therapeutics*, Vol. III, No. August 1954.

17. None

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Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Chemical Pharmacology
LABORATORY
6. Tyrosine Metabolism
PROJECT TITLE
5. NHI-116
SERIAL NO.
7. B. N. La Du
PRINCIPAL INVESTIGATOR
9. PROJECT DESCRIPTION:

Objectives: In the oxidation of tyrosine in liver vitamin C is required to hydroxylate one of the intermediary compounds, p-hydroxyphenylpyruvic acid. The role of vitamin C and the mechanism by which the hydroxyl group is introduced into the aromatic ring have not been established.

Methods Employed: The enzyme system catalyzing this hydroxylation reaction has been obtained in a soluble state from dog and rat liver and has been purified by salt and organic solvent fractionation. The reaction has been followed by chemical, manometric and spectrophotometric techniques.

Major Findings: The hydroxylation of p-hydroxyphenylpyruvic acid requires two protein components and ascorbic acid. The exact role of each protein fraction is not known. L-ascorbic acid can be replaced by several other compounds having about the same redox potential, such as D-ascorbic acid, hydroquinone and 2,6-dichlorophenolindophenol dye. These compounds are all required in their reduced form, presumably to reduce a component in one of the enzymes.

Significance to Heart Research: Hydroxylation is a reaction of general importance; the biosynthesis of tyrosine, "dopa", adrenaline, and thyroxine, for example, requires this type of reaction. The hydroxylation of p-hydroxyphenylpyruvic acid to homogentisic acid is a convenient system to use to study biochemical hydroxylation. The fact that vitamin C is required in this reaction is of further interest since a study can also be made of how this vitamin functions in a specific biochemical process.

Proposed course of project: Continued studies will require further purification of the enzyme systems involved and localizing the position of ascorbic acid in the reaction.

Budget Data Sheet

0. NHL-146
SERIAL NO.

1. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$10,300	1	1	2	.50	1.00	1.50	-
FY 1956	\$10,300	1	1	2	.50	1.00	1.50	-

2. BUDGET ACTIVITY:

RESEARCH

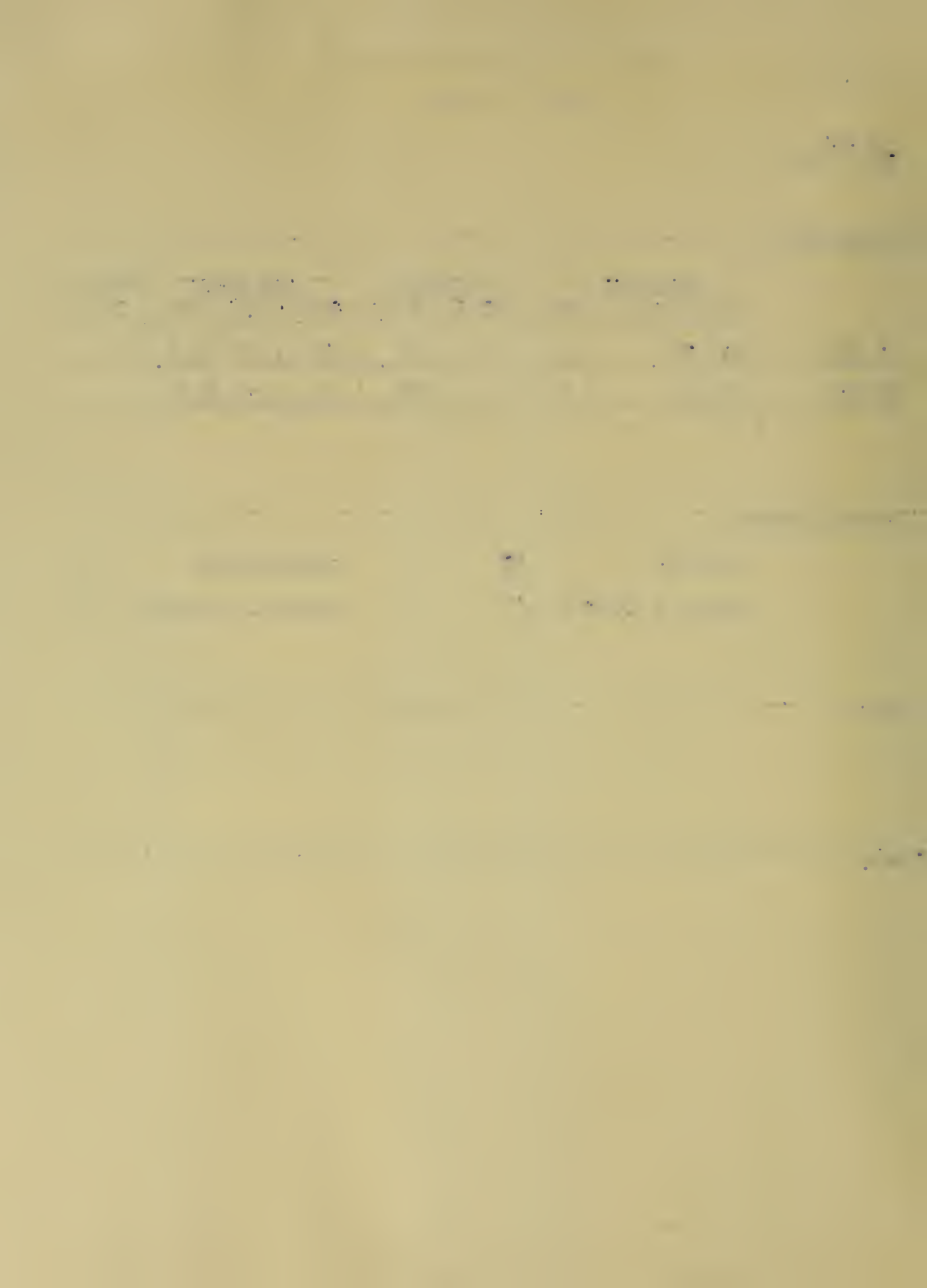
ADMINISTRATION

REVIEW & APPROVAL

TECHNICAL ASSISTANCE

3. None

4. None



R.P.C. - 3
December 1954

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHL-146
SERIAL NO.

16. None

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Research
LABORATORY OR BRANCH

5. NHI-147
SERIAL NO.

6. Office of the Associate Director (In Charge of Research), National Heart Institute
PROJECT TITLE

7. Dr. Robert W. Berlinz
PRINCIPAL INVESTIGATOR(S)

8. J. F. Monahan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The Office of the Associate Director (In Charge of Research) is immediately responsible for the overall planning and direction of the direct research program (laboratory and clinical investigations) of the National Heart Institute, involving about \$3.5 million and a budgeted staff of almost 300 for Fiscal Year 1955. This entails determination of the scope of the research program; selection, organization, and provision of leadership to the professional staff; and review and evaluation of the results of research activities. Continuous study of national and international progress in the field of cardiovascular research is carried out, in order to make certain that the research program of the Institute is of maximum effectiveness in developing knowledge of the causes and methods for prevention and treatment of the cardiovascular diseases.

10. NIH-147
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	\$62,200	2	6	8	2	5	7
FY 1956	\$62,200	2	6	8	2	6	8

12. BUDGET ACTIVITY: Research

13. _____
None

14. _____
None

Honors, Awards, and Publications

15. NIH-147
SERIAL NO.

16. _____
None

17. _____
None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute 2. Technical Services Branch
 INSTITUTE LABORATORY OR BRANCH
3. Epidemiology 4. Framingham, Mass. 5. NHI-148
 SECTION LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.
6. Heart Disease Epidemiology Study
 PROJECT TITLE
7. Thomas R. Dawber, Medical Director
 PRINCIPAL INVESTIGATOR (S)
- George Cytroen, Sr. Asst. Surgeon (R) Douglas E. Bragdon, Sr. Asst. Surgeon
 8. Abraham Kagan, Sr. Asst. Surgeon (R)
 OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Heart Disease Epidemiology Study, Framingham, Massachusetts

Objectives: The objective of this project is to investigate and evaluate those factors which are believed to be significant in the development or the progression of hypertension and arteriosclerotic heart disease.

Methods Employed: In 1950, by random sampling method. 6,535 adults between the ages of 30 and 59 were selected for possible examination. Of these it was possible to obtain the cooperation of 4,494. An additional group of 740 volunteers in the same age range was added to the Study. Those were all given initial examinations with the view toward doing re-examinations at two-year intervals over a long period, during which all the data of pertinent constitutional or conditioning factors will be recorded and analyzed.

Major Findings: In 1954, considerable progress was made in the second, third and fourth examination of the population group under study. The cumulative number of persons examined as of December 31, 1954, is as follows:

<u>Exam</u>	<u>Total</u>	<u>Sample</u>	<u>SK</u>
I	5234	4494	740
II	4821	4081	740
III	2474	1994	480
IV	296	154	142

The project has been set up as a continuing one since it will take a prolonged period of time before major epidemiological findings become available. At present, data on prevalence and incidence of cardiovascular disease is being analyzed.

Analysis of NIH Program Activities
Project Description Sheet

Significance to Heart Research: In order to develop an understanding of the way in which arteriosclerotic and hypertensive heart disease develop it is necessary to obtain vital information regarding the life history of these diseases by observing how and where and in what way they develop. The type of epidemiologic research done by this project will provide this type of information.

Proposed Course of Project: Continued cooperation of the selected sample and volunteer groups is essential to the success of this project. All attempts are continually being made to review and rekindle the enthusiasm of the participants to insure continued interest by them. The problem of follow-up of those persons who have moved away from the Framingham area has now become significant enough so that further action in this direction will be necessary. Direct contact of those persons who have moved to other New England area has been continued and will be carried out in the coming year. Planning as to the best method of follow up of those who have moved farther away will be made shortly.

Completion of the records of those who have died involves considerable work contacting physicians, hospitals, etc. to complete data. Work has begun on this aspect of the program and will be continued.

Planning toward obtaining all possible information about the life habits and characteristics of the population under study is constantly being done with the view towards incorporating new measurements of additional variables which may be related to the development of cardiovascular disease.

The fourth examination includes measurements to determine classification of body build in order that its significance as a factor in coronary disease incidence may be determined. Similarly, additional data regarding total energy output is being obtained.

In the future it is planned to add a nutritional evaluation if this can be arranged.

In this way, it is hoped that before the completion of the project all the possible measurable factors related to development of coronary disease and hypertension will be tabulated.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-148
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$119,500	6	16	22	5	14	19	
FY 1956	121,800	5	15	20	5	14	19	

12. BUDGET ACTIVITY: Research

13. None

14. None

Honors, Awards, and Publications

15. NHI-148
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Significance of Solitary Non-Toxic Thyroid Nodules-Preliminary Report,
N.E. J. MED. 251:970-973 (Dec. 9, 1954).

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Technical Services Branch
LABORATORY OR BRANCH
3. Heart Information Center
SECTION
4. _____
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-149
SERIAL NO.
6. Heart Disease Information Program
PROJECT TITLE
7. Lealon E. Martin
PRINCIPAL INVESTIGATOR(S)
8. C. R. Strom, Evelyn Van Steenberg, Arthur Cosing
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION (SEE INSTRUCTIONS AND SAMPLES)

Project: Carry out a program of professional and public information on heart disease, as specified in the National Heart Act.

Objectives: To provide information on all aspects of heart disease; to promote increased use of present knowledge and research findings; to assist prevention, early case-finding, diagnosis, and treatment of heart disease through lay education; and to keep individuals and organizations in the heart disease field informed as to current developments and the experience of others.

Methods Employed: A wide range of media of communication are utilized. Activities include the preparation and distribution of heart disease information-education articles, leaflets, pamphlets, and other items; planning and development of audio-visual materials, exhibits, radio and television broadcasts and transcriptions; preparation of reports and other special materials; issuance of releases and providing assistance to the press, periodicals, and science writers; maintenance of an inquiry and reference service; and cooperation with other agencies and organizations in planning and executing informational and educational projects on diseases of the heart and blood vessels.

Major Findings: Among the many information-education materials produced and activities conducted during 1954 were:

Exhibits on 1) the Programs of the National Heart Institute--for use at the Second World Congress of Cardiology and other major medical meetings, 2) Progress in Heart Research--for the Miami Health Fair and other public showings, and 3) National Heart Institute Research--a presentation of scientific investigations conducted by the Institute, for various uses.

Reports on Highlights of 1953 Heart Research Progress; Research Progress Reports summarizing advances in Congestive Heart Failure, Arteriosclerosis, High Blood Pressure, Drug Therapy in Hypertension Surgery in Congenital Heart Disease, and the Second World Congress of Cardiology. Items such as administrative reports, budgetary statements, and other special materials were prepared in whole or in part.

Publications. The chief publication issued during the year was a revised edition of the statistical booklet, "Diseases of the Heart and Blood Vessels-Facts and Figures." Published jointly by the American Heart Association and the National Heart Institute, the booklet provides up-to-date information on statistical aspects of cardiovascular disease and constitutes a uniform statement by the government and chief voluntary agency in the field.

In process of preparation are publications to be issued in 1955 in connection with the campaign for prevention of rheumatic fever and rheumatic heart disease. These include a leaflet for the general public, "Stop Rheumatic Fever", a film discussion guide for use at public meetings, and other program materials.

Audio-visuals. A new motion picture, "Stop Rheumatic Fever", was produced and will be released early in 1955 for nationwide health education use. The film shows that rheumatic fever can be prevented by treatment or prevention of strep infections. It is part of a health education unit developed by the Heart Institute and the Heart Disease Control Program (DSHS) in cooperation with the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. Initial distribution of the film to health departments will be made by the Public Health Service. The Heart Association is cooperating in general distribution, and the film will be made available for purchase at an unprecedented low cost.

Releases and services to writers were important facets of public information activities. In addition to regular releases, such as those reporting grants and awards, lecture announcements, or newsworthy appointments, special releases were made to professional journals and science writers on specific research accomplishments by Institute scientists. In addition, many services were given newspapers, magazines, television, radio, and other media of mass communication, through working directly with writers, reporters, and others. As a result, articles on heart subjects appeared in a number of large-circulation outlets such as Time, Life, Newsweek, U. S. News and World Report, Business Week, Saturday Evening Post, Ladies Home Journal, and others.

Informational services were also furnished in connection with various meetings, including the Second World Congress of Cardiology.

Inquiry and reference service was provided as a continuing function in meeting mail, telephone, and in-person requests for information on heart disease subjects from the general public, individuals in medical and health professions, and organizations. Inquiries not answerable by forwarding of suitable publications or other already available material required special compilation of references or information.

Special Programs:

Rheumatic Fever: Development of a nationwide campaign for rheumatic fever prevention with initiation of an intensified professional and public educational program beginning in January and continuing as a major activity of the year; establishment of this campaign as a joint program with American Heart Association and Heart Disease Control Program (DSHS); implementation of the campaign through NIH, PHS, and DHEW support and endorsement; assistance in implementing other aspects of this program.

Cerebral Vascular Diseases: Planning and development of ideas and materials for programs in this field which, continuing next year, should lead to production and use of much-needed educational materials as well as stimulation of other activities.

Significance to HEART Research:
(Name of Institute)

(Note: The significance of H.I.C. activities to public health heart programs, which is also of major importance, is not included per se in the report form, but some indication of this aspect of H.I.C. responsibilities can be seen in various parts of this report.)

Provides information concerning research development and advances; assists the dissemination of new knowledge; furthers the use of research findings; furnishes consultation and services as needed in preparation of exhibits and other graphics, in clearance and printing procedures, and other matters involving media of communication.

Proposed course of project: This is a continuing operation with its general function specified by law. Informational activities will continue to be conducted in response to needs, with variance in emphasis, content, or media as indicated by program needs. In the coming year, the rheumatic fever program, will receive major emphasis. Also, cerebral vascular diseases, hardening of the arteries, and normal physiology will be stressed. Improvement and expansion of public reporting of research is also planned for the year.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-149
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$77,300	4	4	8	3	4	7	
FY 1956	74,800	4	4	8	4	4	8	

12. BUDGET ACTIVITY: Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NHI-149
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

See under 9.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Lealon E. Martin -- Member, Committee on Education and Public Information of the Council on Community Service and Education, American Heart Association

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE

2. Technical Services Branch
LABORATORY OR BRANCH

3. Biometrics
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NHI-150
SERIAL NO.

6. Statistical Consultation and Research Services
PROJECT TITLE

7. Dr. Max Halperin, Felix E. Moore
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: Provision of consultative services in statistical design and analysis of experiments, with associated research in statistical methodology.

(A) Objectives: The primary objective of this service is to provide assistance in the statistical design, interpretation and evaluation of experimental studies conducted by the scientific staff of the National Heart Institute, and by grantees of NHL.

(B) Methods employed: The assistance described above is accomplished using the standard methods of biometry, statistics and probability, with necessary modifications as required by the problem at hand. Not infrequently standard statistical methods are not available to handle research problems, and it is necessary for personnel of the section to develop new methods.

(C) Major findings: As a service organization, this section primarily assists other investigators in making important biological and medical findings, rather than in making such findings directly. Such assistance is frequently acknowledged in the publication of findings of the principal investigators. Occasionally, the nature of the assistance is such as to warrant co-authorship rather than simple acknowledgement.

(D) Significance for Cardiovascular Research: This is a specialized service which is provided as requested by investigators. As such it makes a general contribution to the increase of the research potential.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-150
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$3,700	2	2	4	1	0	1	
FY 1956	3,700	2	2	4	1	0	1	

12. BUDGET ACTIVITY: Research

13.

14.

15. NHL-150
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Halperin, M., Greenhouse, S.W., Cornfield, J., and Zalokar, J.:
"Tables of Percentage Points for the Studentized Maximum Absolute Deviate in Normal Samples". Journal of the American Statistical Association (in press for publication March, 1955)

17.

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Technical Services Branch
LABORATORY OR BRANCH
3. Biometrics
SECTION
4. LOCATION (IF OTHER THAN BETHESDA)
5. NHI-151
SERIAL NO.
6. Statistical services for Cooperative Study of Lipoproteins and Atherosclerosis
PROJECT TITLE
7. Felix E. Moore, Chief
PRINCIPAL INVESTIGATOR(S)
8. OTHER INVESTIGATORS
9. PROJECT DESCRIPTION:
 - (A) Objectives: To assess the value of various measures of lipoproteins and cholesterol in predicting development of atherosclerotic disease; to measure the association of elevated lipoprotein with various diseases; to provide standard lipoprotein measurements values for normal populations.
 - (B) Methods employed: Four laboratories (at the University of California, Cleveland Clinic, University of Pittsburgh, and Harvard University) have cooperated to secure blood samples from large, representative population groups. Lipoprotein measurements (by the ultracentrifuge) and cholesterol measurements (by the Abell-Kendall method) have been done on approximately 10,000 cases. At the end of two years follow-up status is secured for each case. Results are reported to the Biometrics Research Section which acts as statistical coordinator for the group.
 - (C) Major findings: Earliest reports will become available late in 1955; final reports will probably be available in the first half of 1956.
 - (D) Significance to HEART research: Discovery of a test predictive of cardiovascular disease, and one which would permit assessment of measures for the prevention of atherosclerosis would be of great practical value. This study is testing a procedure proposed for that purpose.

Analysis of NIH Program Activities

Budget Data Sheet

10. MHL-151
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$13,100	2	3	5	1	.50	1.50	
FY 1956	13,100	2	3	5	1	.50	1.50	

12. BUDGET ACTIVITY: Research

13. COOPERATING UNITS, ETC.

Donner Laboratory, University of California; Cleveland Clinic, Cleveland, Ohio; Department of Biophysics, University of Pittsburgh; Department of Nutrition, School of Public Health, Harvard University. The study in these institutions is financed from research grant funds administered by the National Heart Institute.

14.

15. _____

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17.

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Technical Services Branch
LABORATORY OR BRANCH
3. Biometrics
SECTION
4.
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-151
SERIAL NO.
6. Statistical services for Cooperative Study of Lipoproteins and Atherosclerosis
PROJECT TITLE
7. Felix E. Moore, Chief
PRINCIPAL INVESTIGATOR(S)
8.
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION:
 - (A) Objectives: To assess the value of various measures of lipoproteins and cholesterol in predicting development of atherosclerotic disease; to measure the association of elevated lipoprotein with various diseases; to provide standard lipoprotein measurements values for normal populations.
 - (B) Methods employed: Four laboratories (at the University of California, Cleveland Clinic, University of Pittsburgh, and Harvard University) have cooperated to secure blood samples from large, representative population groups. Lipoprotein measurements (by the ultracentrifuge) and cholesterol measurements (by the Abell-Kendall method) have been done on approximately 10,000 cases. At the end of two years follow-up status is secured for each case. Results are reported to the Biometrics Research Section which acts as statistical coordinator for the group.
 - (C) Major findings: Earliest reports will become available late in 1955; final reports will probably be available in the first half of 1956.
 - (D) Significance to HEART research: Discovery of a test predictive of cardiovascular disease, and one which would permit assessment of measures for the prevention of atherosclerosis would be of great practical value. This study is testing a procedure proposed for that purpose.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-151
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$13,100	2	3	5	1	.50	1.50	
FY 1956	13,100	2	3	5	1	.50	1.50	

12. BUDGET ACTIVITY: Research

13. COOPERATING UNITS, ETC.

Donner Laboratory, University of California; Cleveland Clinic, Cleveland, Ohio; Department of Biophysics, University of Pittsburgh; Department of Nutrition, School of Public Health, Harvard University. The study in these institutions is financed from research grant funds administered by the National Heart Institute.

14.

15. _____

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17.

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Technical Services Branch
LABORATORY OR BRANCH
3. Biometrics
SECTION
4. LOCATION (IF OTHER THAN BETHESDA)
5. NHI-152
SERIAL NO.
6. Statistical studies related to Framingham Heart Disease Epidemiology Study
PROJECT TITLE
7. Felix E. Moore, Chief
PRINCIPAL INVESTIGATOR(S)
8. Dr. T. R. Dawber, Director, Framingham Heart Disease Epidemiology Study
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

This project is described in detail in the Project Description sheet submitted for the Epidemiology Section, Technical Services Branch, NHI.

The Biometric Research Section takes responsibility for (a) general statistical planning for the study, (b) final preparation of forms, (c) development of coding procedures, (d) planning of punch card methods and liaison with NIH Statistical Processing Section, (e) preparation of statistical analyses for reports in collaboration with staff of the Epidemiology Section.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-152
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$13,700	2	4	6	1	.50	1.50	
FY 1956	13,700	2	4	6	1	.50	1.50	

12. BUDGET ACTIVITY: Research

13.

14.

15.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17.

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Technical Services Branch
LABORATORY OR BRANCH
3. Biometrics
SECTION
4. _____
LOCATION (IF OTHER THAN BETHESDA)
5. NHL-153
SERIAL NO.

6. Development and Application of Statistical Methods to the Study of
Cardiovascular Disease in Human Populations
PROJECT TITLE

7. Felix E. Moore
PRINCIPAL INVESTIGATOR(S)

8. All professional personnel of Section
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

- (A) Objectives: To seek out and create sources of data on the morbidity and mortality from cardiovascular diseases; to analyse these for the information they provide on the extent of the problem, on the trends in time, and differentials among the age, sex, geographic groups; to explore epidemiological leads provided by these analyses; to prepare materials for dissemination to professional and lay groups in cooperation with associated specialists.
- (B) Methods employed: Available materials are collected from such sources as the national offices of vital statistics (U.S. and foreign), the various collectors of routine morbidity statistics (eg. Armed Forces), and the various groups carrying on ad hoc morbidity surveys (California, Baltimore, Hunterdon County, etc.). In addition, the Section cooperates with groups engaged in special field surveys, assisting them in their planning to the end that needed data can be secured.
- (C) Significance to HEART research: This activity provides investigators with information required as a background for their work, and may provide leads for further laboratory, clinical or field investigation.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-153
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$26,900	3	4	7	2	1	3	
FY 1956	26,900	3	4	7	2	1	3	

12. BUDGET ACTIVITY: Research

13.

14.

15. SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"Diseases of the Heart and Blood Vessel - Facts and Figures", Rev. Edition
Published by the American Heart Association in cooperation with the
National Heart Institute

17.

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute 2. Technical Services Branch
INSTITUTE LABORATORY OR BRANCH

3. Biometrics 4. 5. NHI-154
SECTION LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Study of mortality and disability retirement among railroad workers
PROJECT TITLE

7. Felix E. Moore
PRINCIPAL INVESTIGATOR(S)

8. Dr. William Bann and Mr. William Haenszel, National Cancer Institute
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION: Primary responsibility for this study lies in the National Cancer Institute. NHI is providing some funds and will share in analytical responsibility.

(A) Objectives: To investigate differences in cardiovascular disease rates which may be associated with differences in occupational groups among railroad workers in the U. S.

(B) Methods employed: A cohort of all working and retired railroad employees with at least ten years' exposure in the industry as of January 1, 1953 will be set up (approximately 1,000,000 persons). From its records the Railroad Retirement Board can assemble the population base data and information on mortality and disability retirement for this cohort. A procedure has been worked out to assemble the information from the various sources and reproduce it on a special set of study punch cards, which can be placed at the disposal of the investigators. Sufficient identifying detail has been provided to make possible further studies of groups exhibiting unusually high rates. The Railroad Retirement Board under contract has supplied punch cards for the cohort understudy and is now searching their records and preparing reports on mortality and disability retirement for the first study year.

(C) Significance to HEART research: Railroad employees are an occupationally stable group, with their own retirement system. This is an ideal setting in which to attempt investigation of occupational factors and will provide good experience for later handling occupational data collected in Social Security Board operations. Differences in occupational groups are large enough so that the effort hypotheses can be tested.

Project Description Sheet

- 2 -

- (D) Proposed course of this project for the succeeding calendar year: At least two years mortality experience need to be collected before findings on occupational differentials and mortality can be reported. It is anticipated that mortality and disability retirement experience may be collected over a period of years and that details on specific occupations and exposures to forces of suspecting of influencing cardiovascular diseases.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-154
SERIAL No.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEAR			PATIENT YEARS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$4,000	1	0	1	0	0	0	
FY 1956	4,000	1	0	1	0	0	0	

12. BUDGET ACTIVITY: Research

13.

14.

15. _____

16.

17.

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Bureau of State Services
Division of Special Health Services
LABORATORY OR BRANCH
3. Heart Disease Control Program
SECTION
4. Washington, D. C.
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-155
SERIAL NO.
6. Program Management and Direction
PROJECT TITLE
7. Dr. William H. Stewart
PRINCIPAL INVESTIGATOR(S)
8. Mr. Frank L. Worden
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION (SEE INSTRUCTIONS AND SAMPLES)
 - A. Direction of program and administrative planning and execution.
 - B. Interpretation and dissemination of Departmental, Service, Bureau and Division policies and directives.
 - C. Coordination of medical and general technical and professional consultation services within and outside the Service.
 - D. Serving on in-Service and out-of-Service committees.
 - E. Reviewing and directing the Branch publications program.
 - F. Formulating and executing the Branch's budget.
 - G. Direction of staff training and development.
 - H. Planning and directing effective application of results from operational studies and investigations.
 - I. Develop and maintain a close working relationship with National Heart Institute, Children's Bureau, Office of Vocational Rehabilitation, American Heart Association, and others whose activities have an impact on the total heart disease control program.
 - J. Plan with Regional Offices to encourage and assist States to engage in operational research studies to evaluate existing methods and techniques now being used and to stimulate the development of projects that will test the application of research findings in a public health situation to determine their practicability and effectiveness.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-155
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	29,000	2	2	4	2	2	4	
FY 1956	29,000	2	2	4	2	2	4	

12. BUDGET ACTIVITY: TECHNICAL ASSISTANCE

13. NONE

14. NONE

15. NONE

16. NONE

17. NONE

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Bureau of State Services
Division of Special Health Services
LABORATORY OR BRANCH
3. Heart Disease Control Program
SECTION
4. Washington, D. C.
LOCATION (IF OTHER THAN BETHESDA)
5. NHL-156
SERIAL NO.
6. Program Services
PROJECT TITLE
7. Dr. Clarke W. Mangum, Jr.
PRINCIPAL INVESTIGATOR(S)
8. _____
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION:

PROGRAM SERVICES SECTION1. Development of Nuclei Training Centers

A center which will serve as a nucleus for training will be established as a method for improving on-going educational experiences for nurses giving services in heart disease in hospitals and public health agencies, utilizing already existing clinical and other facilities. This center will be established as a pilot study to determine whether this is a successful way to provide adequate training for nurses working in the cardiovascular field.

2. Participation with the American Heart Association and National League for Nursing in a Joint Committee on Nursing Education

In joint action with the American Heart Association working through the professional staff of the National League for Nursing, establish a committee of representative experts in heart disease nursing to develop educational materials and guides with professional content to be used in schools of nursing and in other nursing education situations.

3. Evaluation of Patient Dietary Booklets Concerning Sodium Restricted Diets

In cooperation with the American Heart Association, American Medical Association, American Dietetic Association, evaluate the utilization of the booklets, "Food for Your Heart," and "Planning Low Sodium Meals," for the purpose of either revising one or both booklets or preparing a new one. This is being carried on by the nutritionists and the social psychologist on the staff.

4. Pilot Study of Special Community Nutrition Service

The purpose of this study is to determine to what extent dietary instruction services will be utilized by patients under medical supervision in an area where these services are not available for all patients. In cooperation with a local health department and a medical society nutrition services will be offered to physicians and clinics in the area to determine the method for developing the service. Utilization of nutrition services and acceptance by the community will be evaluated periodically and the methods being used for the presentation and development of nutrition services will be related to the cost.

5. Development of a Guide for the Analysis of Nursing Aspects of the Heart Disease Program

To develop a schedule to be used for analyzing State-wide and/or local heart programs in relation to nursing. This schedule will be used by regional and State consultant nurses for program evaluation and planning.

To prepare a guide for the analysis of the activities carried on by public health nurses in relation to health guidance including casefinding, prevention, and nursing care in heart disease in a generalized program; to test the application of the guide in the field in cooperation with the regional nursing consultant, State and local supervisors.

6. Records and Statistical Consultation to State and Local Health Departments and to Other Agencies

Upon request, assist with record systems and statistical problems and plan for the evaluation of various phases of activities carried on in conjunction with the control and treatment of cardiovascular diseases. This includes the development of records, forms, and procedures for casefinding programs, evaluation of activity in cardiac homes for children, and the development of forms and record procedures for use in rheumatic fever prevention programs and cardiac clinics.

7. Professional and Lay Education

In cooperation with the National Heart Institute, the American Heart Association, and the Technical Services Section of the Division of Special Health Services to develop means for the orderly collection, evaluation, and distribution of audiovisual and other training aids or devices.

To participate in work conferences and institutes for the purpose of assisting State and local communities to include heart disease in their in-service education programs for all professional categories.

8. General Consultation

Continue to give direct consultation to States in cooperation with the regional office consultants on specific aspects of heart programs, including medical, nursing, nutrition, social service, statistics, health education, rehabilitation, and others as indicated. Encourage and assist States to evaluate their program activities to establish their value in combating the problem of heart disease, and to experiment with new ideas or accepted techniques which may have a place in a heart disease control program.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHI-156
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	185,600	18	8	26	18	8	26	
FY 1956	185,600	18	8	26	18	8	26	

12. BUDGET ACTIVITY: TECHNICAL ASSISTANCE

13. NONE

14. NONE

15. NONE

16. NONE

17. NONE

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Heart Disease Control Program
Division of Special Health Services
Bureau of State Services
LABORATORY OR BRANCH
3. Operational Research
SECTION
4. Washington, D. C.
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-157
SERIAL NO.

6. See # 9
PROJECT TITLE

7. _____
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Relationship of Nutritional and Medical Status
of Older Persons to Subsequent Five-year Morbi-
dity and Mortality Experience, San Mateo County,
California

There is an obvious need for research in the field of human nutrition for our aging population, particularly as it relates to the development of chronic disease. Further, there is need for research on the relationship of various physiological and laboratory measurements as they relate to subsequent development of chronic disease. Such research should lead to the development of sound programs for the prevention and early detection of chronic disease.

In 1948, 577 persons between the ages of 50 and 90 in San Mateo County, California, were given examinations, including detailed nutritional and medical history, physical examination and laboratory studies. Useful data could be derived through a follow-up on these 577 persons during the year 1954 for subsequent morbidity and mortality to determine its relationship to these initial findings.

It is proposed to determine the current and intervening health status of these 577 persons by a search of mortality records on file in the California State Health Department by personal interview with survivors and verification of illness reported by survivors by checking with their private physician. The interview will be done by a nurse through home visits, if necessary, following a questionnaire.

This study will be carried out in three stages: a) study of mortality experience since 1948, b) interview of survivors to determine intervening health status, c) verification of illnesses reported by survivors by checking with their private physicians (where named).

Project Description Sheet

A preliminary report on the mortality experience since 1948 as it relates to the 1948 examination reveals an expected direct relationship between overweight and cardiovascular deaths, an inverse relationship between caloric intake and mortality from cardiovascular disease, between protein intake and mortality from cardiovascular disease, between fat intake and mortality from cardiovascular disease, between carbohydrate intake and mortality from cardiovascular disease. One point of interest is an inverse relationship between total cholesterol and mortality from cardiovascular disease.

Evaluation of a Procedure for Weight Reduction

If cardiovascular-renal diseases are induced by or adversely affected by overweight then reduction of overweight would tend to reduce morbidity and mortality from cardiovascular-renal diseases. We need to find a means of weight reduction which would not only insure immediate weight reduction but should result in maintenance of this weight reduction.

Since 1950, various methods of weight reduction through group meetings have been investigated by the staff at Herrick Memorial Hospital. As the result of experimentation on approximately 300 overweight people participating in group weight reduction meetings, a procedure has been defined which shows promise both from an administrative standpoint of achieving immediate and lasting weight reduction. It is recognized, however, that persons responding for the weight reduction groups thus far conducted at Herrick Memorial Hospital were strongly motivated to do something about their excess weight (as evidenced by their responding). It is necessary to determine, therefore, whether the group "therapy" actually affected the weight reductions observed or whether these weight reductions occurred as a result of the motivation which initially caused persons to respond to the announcement of the weight reduction classes.

It is proposed to recruit 150 obese persons for the formation of weight reduction groups starting in 1954. These 150 obese persons will be divided at random into two parts - 75 to participate in a group weight reduction program and 75 to be held as controls. These two groups will be made comparable as to age, length of time overweight, and degree of overweight. The effect of the group weight reduction method chosen will be measured in terms of the percentage of the group losing optimum excess weight or more (as measured by a performance index) at the end of ten weeks and at the end of one year. Both persons in the test group and in the control group will be weighed at the end of ten weeks and at the end of one year.

Weight reduction was about the same in the two groups at the end of 10 weeks.

Evaluation of Chest X-rays for the Identification of Heart Disease and Hypertension

Each year nearly 15 million chest x-rays are given for the detection of tuberculosis. The extent to which these x-rays are capable of sorting out heart disease and hypertension is not known. Studies conducted in connection with the Boston city-wide chest x-ray survey, suggests that much additional heart disease could be identified if films were read with a higher index of suspicion or if films were read by physicians especially trained in the identification of abnormal heart shadows. Since the routine chest x-ray involves only a single view and thus can detect only post anterior abnormal heart shadows, it would appear that the addition of a lateral chest x-ray should further assist in the identification of heart disease and hypertension.

Analysis of NIH Program Activities

Project Description Sheet

Since 1947, approximately 2,000 executives have been processed through a diagnostic clinic located at White Sulphur Springs, West Virginia. These executives have been sent by their companies as part of a program to prevent premature death through early detection of disease and, in particular, cardiovascular disease. The diagnostic procedures employed are modern and it can be assumed that, at least within the limits of the present knowledge, the diagnostic procedure succeeded in sorting out all of those executives with cardiovascular disease.

As part of the diagnostic procedure, a P.A. and a lateral 14 x 17 chest x-ray have been taken at the 72" distance. It is proposed to reproduce the 14 x 17 chest x-rays representing the latest examination for some 2,000 persons thus far diagnosed and to have these re-read for cardiovascular disease. X-rays will be copied on 70mm roll film with P.A. views making up one set of rolls of films and lateral views making up another. P.A.'s and laterals will carry the same case number. These will then be read by a radiologist, well trained in the identification of abnormal heart shadows. The first reading will be made only on P. A. views and the reader will be rated in terms of his sensitivity and specificity for heart disease and hypertension. A second reading will be made, utilizing both the P.A. and lateral and the reading will again be rated. All diagnoses available on the group of 2,000 individuals will be given on etiological classification and a modified anatomical classification based upon the "nomenclature and criteria for diagnoses of diseases of the heart and blood vessels", New York Heart Association.

During the year all records were abstracted, coded and data put in punch cards. Films were read twice and were marked for heart volume determinations.

Study to Determine the Significance of Cardiovascular Abnormalities Discovered as the Result of Chest X-ray Surveys

The popularity of x-ray screening for chest disease makes it important to obtain information as to the significance of the various abnormalities noted. In particular, the significance of various types of cardiovascular abnormalities noted on x-rays, when other information available for each patient is taken into consideration, needs to be determined so that proper emphasis can be placed in the application of therapeutic measures and investigations.

The occurrence of death associated with x-ray abnormalities probably reflects the most precise evidence available regarding the significance of x-ray findings. It is proposed, therefore, to evaluate x-ray findings and other information available on a group of 10,899 persons, considered as having cardiovascular abnormalities on 70mm x-rays taken in the Los Angeles County Chest X-ray Survey conducted in 1950, by determining which of these persons died from causes presumably associated with these abnormalities during the 3 1/2 years following the chest x-ray survey.

The mortality experience for 3600 males having a cardiovascular abnormality in the 1950 Los Angeles chest x-ray program was determined. During a 2 1/2 year period 11% died of cardiovascular diseases. In the age group 35 to 54 the observed mortality (from cardiovascular diseases) was 12 times the expected - ranging from 9 times the

Activities of NIH Program Activities

Project Description Sheet

expected for arteriosclerotic heart disease to 51 times the expected for rheumatic heart disease. It was agreed with the California State Health Department and interested persons in Los Angeles that females with positive chest x-rays should be similarly checked as well as persons having negative chest x-rays before any data are published. Arrangements were made to have this done utilizing local resources.

Job Requirements and Work Capacity of Persons with Cardiovascular Disease

The project entered the final phase and was successful in obtaining a satisfactory number of cardiacs for examination on the job and in the laboratory. A detailed progress report has been prepared for review by the advisory consultants to the study and plans were made for a final meeting at which time recommendations will be obtained for the preparation of reports for publication and to consider possible extension of the project.

Evaluation of 70mm X-ray for Cardiovascular Disease PD-PA-110

Diagnostic data inadequate. Will be picked up when other diagnostic data becomes available.

Study of the Value of Heart Disease Casefinding through X-ray

At the present time there is much screening for disease and abnormalities through the use of chest x-ray. The rationale for such screening is based partly on the assumption that casefinding enables early treatment which in turn alleviates the condition, prevents or delays progression, facilitates restorative services, and thus increases life expectancy.

The hypothesis that this is so has not been put to the test and the value of early casefinding has in the past been accepted on the basis of general knowledge of the course of disease. Acceptance of chest x-ray programs as a public health measure for heart disease in particular, have been retarded because of the absence of experiments which would bring direct proof to bear upon this hypothesis. For this condition, it is frequently argued that the current level of medical knowledge is not such that individuals identified by chest x-rays can be benefited.

Rolls of 70mm chest x-ray film (200,000 films) taken on the Los Angeles County Chest X-ray Survey conducted in 1950 and the Dallas Texas survey conducted in 1952 will be re-read. Experience in dual reading of chest x-rays indicates that there are undoubtedly many conditions which were missed when the films were initially read. Thus, these films should, if re-read, identify many persons with disease in 1950 and 1952 who were not so advised. Re-reading will produce three groups of positive x-ray films: a) Suspected by 1st reader only, b) suspected by both readers, c) suspected by 2nd reader only if x-rays are re-read with the same criteria and level of suspicion as was used in the original reading, persons in group A should be the same kinds of persons with the same kinds of abnormalities as persons in group C—with the single exception that persons in group A

Analysis of NIH Program Activities

Project Description Sheet

were followed up in 1950 and 1952 (usually for the condition suspected on the 70mm x-ray) whereas persons in group C were not so followed. If those persons in group A fared better since 1950 and 1952 than those persons in group C the hypothesis that x-ray contributes to the control of any or all of the conditions suspected on the x-ray film can be considered supported.

Readers were recruited, trained and study initiated.

Analysis of NIH Program Activities

Budget Data Sheet

10. NHL-157
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$75,400	8	7	15	7	6	13	
FY 1956	75,400	8	7	15	8	6	14	

12. BUDGET ACTIVITY: Technical Assistance

San Mateo County Health Department, California State Health Department, Herrick Memorial Hospital, Greenbrier Clinic, White Sulphur Springs; Los Angeles Tuberculosis Control Foundation, Lockheed Aircraft Corp., Cedar of Lebanon Institute for Medical Research,

14.

15.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Screening for Cardiovascular Disease in a Community by Walter O. Blanchard, William J. Zukel, Ernest M. Morris, Mary Alice Smith and Daniel A. Sullivan in New England Journal of Medicine, September, 1954.

Estimated Prevalence of Overweight in the United States by Sidney Abraham, Analytical Statistician, in Public Health Reports, November, 1954.

17. None

Analysis of NIH Program Activities

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Grants and Training Branch
LABORATORY OR BRANCH
3. _____
SECTION
4. _____
LOCATION (IF OTHER THAN BETHESDA)
5. NHI-158
SERIAL NO.
6. Review and Approval of Research and Training Grants
PROJECT TITLE
7. Dr. J. Franklin Yeager
PRINCIPAL INVESTIGATOR(S)
8. Dr. Murray Goldstein, Dr. Helen Kean, Kathleen Harlow, Jeanne Walton
OTHER INVESTIGATORS
9. PROJECT DESCRIPTION (SEE INSTRUCTIONS AND SAMPLES)

Research Grants

The Heart Institute was appropriated \$7,750,000 for grants for research projects for fiscal year 1955. Through January, 1955, 920 applications for research grants have been received. Of these, 653 were approved for a total of \$7,196,000. In the February, 1955, National Advisory Heart Council Meeting, it is anticipated that some 180 competing applications will be considered for approval. The \$554,000 remaining available will provide funds for payment of about 47 grants.

Teaching Grants

In fiscal year 1955, \$2,362,000 are available for grants for teaching of medical subjects. During the first half of the year 105 grants were approved amounting to \$2,288,000. It is anticipated that the remaining funds will be utilized for grants pending consideration in the February meeting of the National Advisory Heart Council.

Training Stipends

Awards totaling \$220,000 for 68 traineeships have been approved during the first part of fiscal year 1955. Of the \$400,000 available at the beginning of the year, there is a balance of \$178,000 to provide for 60 applications pending action by the National Heart Institute Traineeship Board.

Analysis of NIH Program Activities

Budget Data Sheet

10.
SERIAL NO.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	\$102,000	5	9	14	5	8	13	-
FY 1956	100,800	5	9	14	6	8	14	-

12. BUDGET ACTIVITY: Review & Approval

13. None

14. None

Honors, Awards and Publications

15.
SERIAL NO.

16. None

17. None

Project Description Sheet

1. National Heart Institute
INSTITUTE
2. Administration
LABORATORY OR BRANCH
5. NH-151
SERIAL NO.
6. Office of the Director, National Heart Institute
PROJECT TITLE
7. Dr. James Watt, Director; Robert H. Grant, Administrative Officer
PRINCIPAL INVESTIGATOR(S)

8. None

9. PROJECT DESCRIPTION

The Office of the Director is responsible for the planning, development and management of the total Institute program involving \$16 million during fiscal year 1955. The activities of the Heart Institute is nationwide in its scope and is concerned with four major areas: (1) extramural programs (Grants and Training), (2) intramural programs (laboratory and clinical research), (3) technical services (Heart Information, Biometrics, and Epidemiology) and (4) technical assistance to States (assisting states and other agencies in the use of the most effective methods of prevention and treatment of heart disease).

This Office is responsible for the coordination of the total program involving over 400 positions toward a common goal of improving the health of the people of the United States through these various functions in relation to cardiovascular disease.

Analysis of MIT Program Administration

Budget Data Sheet

10. SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	\$67,000	2	10	12	2	9	11	-
FY 1956	67,000	2	10	12	2	9	11	-

12. BUDGET ACTIVITY: Administration

13. None

14. None

Honors, Awards, and Publications

15. SERIAL NO.

16. None

17. None

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