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11-4-1-98

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Semi-Annual Progress Report
N5-Ori-76, Project XIII

NAV1.941208.094

INTRACELLULAR CHANGES

IN

TRAUMA, DEPLETION AND REPAIR

with

Special Reference to Burns

Covering the Period from 1 January 1953 to 30 June 1953

Submitted on 29 July 1953

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School at the Massachusetts General Hospital

Part I. Introduction

During the ~~period covered by this semi-annual progress report, 1 January 1953 through 30 June 1953,~~ past year under this the work ~~of~~ the ~~Task Order~~ has continued to deal with problems of the burned patient. Progress is being made in basic understanding leading to improved practical management of the severely burned patient. The place of whole blood in burn therapy, for example, can now be described with greater authority and this is a pressing problem in the planning for disaster management.

The base of investigation has spread once again from burns to other fields. New clues have suggested a shift in emphasis. The aminoaciduria and creatinuria observed in the burned patient makes it wise to find out where else in trauma and surgical disease comparable nitrogen excretion may be found; a wide search is in full swing. The course of the eosinophils in the burned patient is not satisfactorily explained solely by the glandular upheaval resulting from the trauma; here again a search is advisable to see where similar changes may be found and a lead obtained as to the physiologic meaning of the eosinophilia.

A steady flow of burned patients, ample for investigative needs, has continued to come to this hospital. In the last thirteen months 116 burned patients have been cared for by the personnel of this research unit at the Massachusetts General Hospital. The number of patients places a heavy work load of patient care upon our group of investigators. The load encroaches upon time for investigation but it cannot be managed otherwise. Investigations of wound management and metabolic derangements demand that the investigator also assume responsibility for other aspects of patient care. If patient care and investigation are divorced, there is too much of a chance that the patient will suffer. The investigator may also not be aware of the vagaries of the patient's condition and fail to make due allowance for each in his conclusions.

The patients with conditions other than burns who have been studied, include those with problems of plastic surgery requiring skin grafting, with disease of the adrenal cortex requiring adrenalectomy, those requiring other operations and a few with major fractures. These patients also are under the charge of members of the investigative group. A considerable portion of the investigative work continues to be done in the experimental laboratory.

Part II. Studies -- Progress Made.

The studies carried out are divided into the following categories: Wound Healing, Shock, Metabolism, Infection and the Consequences of Perforation of a Peptic Ulcer.

A. Wound Healing.

1. <u>The Effect of Temperature and Humidity on the Rate of Wound Healing</u>. Drs. Cannon, Minor and Bascom. This project is organized to obtain basic information bearing upon the problem of the open versus the closed method of treating burn wounds. The rate of epithelial regeneration is being observed in the non-infected, controlled, experimental wounds of patients under varying conditions of temperature and humidity. Split thickness grafts of identical thickness and size are removed from each thigh of patients who need skin grafting for one or another reason. The dressing to each thigh is identical. One thigh is maintained in a controlled environment by means of a bedside air conditioning unit; the other thigh is cared for under room air conditions. The healing of the two thigh wounds is compared.

The rationale behind this investigation is as follows. Bacteria flourish in a warm, moist environment. The burn wound under a thick dressing is warm and moist. That treated by the exposure method is relatively dry and cool. The open method of treating a burn therefore should impede bacterial generation and growth.

On the other hand, the regeneration of epithelial cells may also be influenced

by the temperature and humidity of the environment. The rate of epithelial regeneration may be slower in the cool wound and the spread of the epithelium may be impeded under dry conditions. The advantages of the open method of treating the burn wound gained in regard to bacteria may be lost in relation to epithelial cell regeneration. The advantages and disadvantages of the two methods of treating burn wounds therefore may cancel each other out.

A lot is known about the influence of temperature and humidity on bacterial growth, but little about epithelial regeneration and wound healing beyond the indirect information gained from tissue cultures.

An advantage of our experimental approach in the patient is that infection is essentially eliminated. It is virtually impossible to manage the wounds of experimental animals under comparable bacterial control.

The observations are tedious, time-consuming, and only an accasional patient is suitable. We have nothing as yet to report but the observations are underway.

2. The observations on wound healing in Cushing's disease and other projects mentioned in the previous reports have either been completed or are in abeyance.

B. Shock - Fluid Therapy.

1. Whole Blood versus Plasma as the Colloid Therapy of Choice. When discussing this problem of burn therapy about which there has been considerable dispute it is essential at the outset to define what we are talking about. Whole blood is badly needed in the therapy of almost all severely burned patients. Anemia develops rapidly in patients with extensive, open, infected wounds. This anemia in our opinion is due to the infection and repeated replacement of red cells by transfusion is essential to good therapy. The need for transfusion comes as infection develops in many patients. This is apparent well within the first week after injury and continues until the wounds are covered with skin and the infectious process is in abeyance. No one disputes this need for whole blood transfusion. What is in

question is the amount of whole blood needed in the therapy of the severely burned patient in the first 48 hours -- the so-called shock phase of burn therapy. The need for whole blood at this time depends logically upon the volume of red cells destroyed by the heat -- those hemolyzed immediately and those sensitized and undergoing subsequent hemolysis.

The question of the colloid solution of choice to be used in the prevention or therapy of burn shock is a critical one both for the Armed Forces and civilian defense. If, as some believe, whole blood is an essential part of the initial therapy of the extensively burned patient, then means will have to be found to increase the availability of whole blood in war areas and in civilian areas threatened with atomic bomb attack in order to treat extensively burned casualties. If, however, plasma is equally or nearly as good as whole blood, then the problem of supply and storage is facilitated. What whole blood is available in an area of disaster could be reserved for those casualties who have suffered true whole blood hemorrhage, the burned patients being treated with plasma or a plasma expander. Because of the logistic importance of this question we have continued to push the investigation relating to this problem during the course of these last six months.

The history of the development of the different points of view regarding the colloid solution of choice in the therapy of burn shock is worth reviewing. Otherwise it is hard to understand why some take the position that the best therapy is a combination of plasma and electrolyte solutions while others believe that whole blood should be used instead of the plasma or a plasma expander. The difference of opinion stems from a different interpretation of the validity and meaning of measurements made in burned patients and mortality studies in burned animals.

During the early part of World War II a combination of plasma, isotonic electrolyte solution and water emerged as the best fluid therapy for the burned patient in the first two days after injury. Whole blood was to be given in small quantities in the first two days to replace those red cells destroyed by the burn and later in larger quantities as signs of anemia developed. Extensive studies were carried out at this hospital and elsewhere, notably Glasgow, and Birmingham in England, which indicated that at most from 7 to 10% of the red cell mass was destroyed by the heat at the time of the burn. The Evans Blue dye method was the one used for these measurements; this method was then and subsequently has been open to question. (See Moore, Peacock, Blakely, and Cope, Ann. Surg. 124:811,1946; and Colebrook, L. et al, Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43. Published 1944.)

In 1944 Moyer, Coller et al (Ann. Surg. 120:367) reported studies on survival of severely burned dogs indicating that a combination of defibrinated whole blood and an electrolyte solution gave a more prolonged survival than plasma and electrolyte solution. The number of dogs in each series of experiments was small. Survival time of burned dogs is notoriously variable and we have always wondered whether the results would not be somewhat otherwise if the experiments of Moyer were extended to a larger series.

Near the end of World War II studies made here using radioactive iron tagged red cells to measure the red cell mass confirmed the earlier observations using the less accurate plasma-dye method. (See above, Moore, Peacock, Blakely, and Cope reference.) More recently, 1950, Evans and others have tackled the problem using P^{32} tagged red cells. As high as 43% destruction of the red cell mass has been reported. Puzzled by the discrepancies between our own observations, those of Moyer and Coller and of Evans, we have reexamined the question using two new approaches.

a. Radioactive Chromium Tagged Red Cells in the Measurement of Red Cell Destruction. Drs. Baker and Rovit have adapted the radioactive chromate method of tagging red cells to the measurement of red cell destruction by the burn. The

method was developed by Drs. Sterling and Gray of the Harvard Biophysical Laboratory and offers the best method thus far found for the measurement of the red cell mass in the burned patient. The manuscript by Raker and Rovit describing their trial of the method and its use in experiments with burned dogs is given as Appendix A.

Raker and Rovit confirm that the chromate ion forms a firm bond with the red cell without destroying the red cell. The bond is formed quickly within a half hour. The chromium attaches itself to the globin. If the red cell is hemolyzed by a burn, it sticks to the globin in the plasma. The concentration of chromium in the plasma can thus be used as a measure of hemolysis following a burn in an experimental animal injected with chromium tagged red cells prior to burning. This is the first way in which the chromium tagged cells quantitate the red cell destruction. The second way is by giving a second injection of the tagged cells after the burn and comparing this second volume with the pre-burn volume. It is thus a double check method and good correlation has been observed.

This method has proved better than the radioactive phosphorus method for tagging red cells. We suspect from our own observations that the phosphorus is not bound securely enough for use in investigating this problem. Phosphate is a physiologic ion passing constantly in and out of the red cell. It therefore may not stay in the original tagged red cells when injected into the test object but can pass out again into the plasma. The initial excess of the phosphate in the plasma is also difficult to wash from the cells in preparing the red cells for injection.

In their experiments with dogs Raker and Rovit found that a burn of 50% of the body surface, of moderate intensity, gave an average red cell destruction of 8% of the red cell volume before injury. This thermal injury is believed to be comparable to that observed in a chance severe burn of the human being.

When the severity of the burn was increased to a deep cooking burn, then the destruction of the red cells reached 40% of the red cell volume. This type of severe, deep burn is rarely encountered in the human being. The injury of flash burns, hot water burns, and indeed those of burning clothing rarely penetrate deeply beneath the skin. Only high voltage electrical burns penetrate deeply and these rarely extend to more than one or two extremities.

The percentage of red cell volume destroyed in these two experiments is what one would have predicted from the amount of blood circulating in the burned tissues. Only a small proportion of the body's blood is in the skin or immediately beneath it. Therefore if all of the red cells touched by the burn are destroyed, if the burn is limited to the skin, only a small proportion of the body's red cells will be hemolyzed. If on the other hand the heat reaches into the deeper recesses of the body, it will obviously reach a greater proportion of the red cells and a greater proportion of the total volume will be destroyed. (See Appendix A.)

We have, of course, been using the chromium method to measure the red cell destruction in burned patients. By the time of the last report 9 patients had been so studied. On the basis of the probable red cell mass before injury it was estimated that not over 10 to 12% of the red cell mass had been destroyed by the extensive burn. It has been possible to measure only 2 more patients since that report. The observations on these patients are in line with the earlier ones. We feel that more observations will be needed before having an adequate experience to publish the material, but it is our impression at this time that the observations in the patients are in line with the experimental work being recorded by Raker and Rovit. (Appendix A.) Since the observations agree with those made earlier, during World War II, we feel that the current trend toward the use of whole blood in the shock therapy of the extensively burned patient could well be reviewed.

b. Blood Viscosity and Blood Flow in the Critical Evaluation of Whole Blood Therapy. The hematocrit of the blood rises as a result of a burn. If whole blood rather than plasma is used as the colloid replacement therapy of the burned patient, the high hematocrit is maintained or further elevated.

It has been demonstrated by Seligman, Blalock and their colleagues that in a variety of experimental conditions the viscosity of the blood varies directly with the hematocrit. This has been found to be true in experimental and human burns by Dr. Quinby. The article describing this work has been published in Surgery and reprints were submitted as technical reports during the period covered by this report.

It has remained to be shown whether the more viscous blood retards blood flow and endangers the function of the essential unburned organs such as liver, brain, and kidney. Even if the blood flow is retarded by the increased viscosity it must be recognized that the more viscous blood with its high hematocrit has a greater than normal oxygen carrying capacity. Such increased oxygen capacity could permit greater oxygen utilization by the tissues and although the blood flow was reduced the tissues might receive the same amount of oxygen.

This problem of blood flow was first attacked by Dr. Quinby in burned dogs. He tried to measure the blood flow to the brain by quantitating the blood flowing out of the severed internal jugular vein. He did find that the blood flow of the more viscous blood was indeed reduced and that the oxygen utilization from each cc. of blood was increased. The results of the experiments varied, however. In some the oxygen utilization was equal, in others reduced.

The variability of the blood flow method employed by Dr. Quinby was so great that we were unable to draw any conclusions from the experiments. This approach has therefore been abandoned.

Dr. Nardi has taken up the problem from a different point of view. He is measuring the blood flow through the liver, and because of the method he is em-

ploying he has been able to proceed directly to measurements in the human being. An account of the method used and of the experiments thus far carried out is given by Dr. Nardi in Appendix B. It is considered particularly fortunate that a method should now be available for observing liver blood flow and that Dr. Nardi is taking on this problem in the burned patient. The liver has long been neglected as an organ to be investigated following trauma such as a burn. Dr. Nardi is making a start on liver function by this approach and also by that using S^{35} tagged amino acids, to be recounted under Metabolism.

2. Posterior Pituitary Activity in Burn Shock. There is much to suggest that the posterior pituitary gland is actively secreting its antidiuretic hormone following the trauma of a burn. The specific gravity of the urine in our patients remains high in the first days after injury even when the fluid therapy is apparently adequate or more than adequate. In a normal individual given fluid more than adequate for his needs, the specific gravity of the urine falls. The experiments of Verney of Cambridge, England, suggest that there should be an output of antidiuretic hormone in response to the pain of the trauma and to any dehydration developing secondary to the injury. These two would account for the secretion of antidiuretic hormone in the initial hours. Continued secretion of the antidiuretic hormone might well interfere with the unloading of the extra fluid given as therapy during the phase of edema resorption. This second phase which starts after the thirty-sixth hour appears frequently to give trouble in the extensively burned patient, leading to generalized edema and occasionally pulmonary edema. If the secretion of the antidiuretic hormone could somehow be cut off, elimination of the excess fluid could be facilitated and water-logging prevented. In both phases, that is the initial phase of dehydration and development of edema, and the subsequent phase of edema resorption and water-logging, it should be important to know what the posterior pituitary is doing. We have long had this problem in mind. The arrival of Dr. Bascom as Research Fellow now makes this possible.

We are particularly fortunate in having Dr. Alexander Leaf of the Department of Medicine as an advisor and collaborator in this project. Dr. Leaf has been studying the antidiuretic hormone activity in various medical conditions and he has recently obtained exciting evidence of a volume receptor control of the posterior pituitary output. (See Alexander Leaf, J. Clin. Invest., 31:54,1951; 31:60,1951; and 31:914,1952.)

3. Edema Volume and Need for Sodium in the Shock Therapy of the Burn Patient. Drs. Raker and Minor. This is a project which was started in December 1952. The reasons for the project were given in the last semi-annual progress report. In brief, we are dissatisfied with our knowledge regarding how much sodium to include in the fluid therapy of the burned patient. Rosenthal et al, Fox and others believe that the all important element to the shock therapy of burns is the sodium ion. Drs. Butler and Talbot of our Pediatrics Staff on the other hand have the idea that since all sodium that is given as therapy in the initial hours after injury must subsequently be excreted through the kidney, we should be sure to give the minimum in order to facilitate the kidney's subsequent problem. This suggestion arose as a result of two fatalities and two near fatalities in burned children treated in collaboration by this research group with Drs. Butler and Talbot.

Our own point of view has been a median one. We have postulated that the important thing in the shock therapy of the burned patient is to maintain a normal environment for the unburned tissues and organs. The wound is a parasite and beyond our control; therefore we feed the patient what the wound robs and in regard to sodium we have tried to give neither too much nor too little.

It has seemed wise to reinvestigate the sodium need and from a new angle. Raker and Minor are measuring the distribution of sodium in the unburned portions of the body, both extra and intracellular, which results from therapies of high, medium, and low sodium. The experiments are being carried out on burned dogs and

include tissue biopsies as well as the radioactive sodium space measurements. The investigations are only in their initial phase.

4. Do Pressure Dressings Effectively Diminish the Need for Fluid Therapy? In World War II it was an accepted principle of burn therapy that pressure dressings should be applied to the head and extremities of the burned patient in order to diminish the fluid needed as therapy or in prevention of burn shock. This attitude had many early backers and seemed well supported by experimental evidence of Siler and Reid, Glenn and Drinker, and others. The impression of many clinicians fell in with the experimental evidence and the principle became accepted.

With the recent swing toward open therapy of the burn wound initiated by Wallace, Blocker and Pulaski, the possible value of the pressure dressing in sparing fluid seems to have been lost sight of. Has this been wise? Are we forgetting something important? In seeking simplicity of the care of the wound are we adding to our troubles in the fluid therapy of the burned patient?

Two years ago Dr. Vilain, a French research fellow in plastic surgery, was assigned this problem of testing the efficacy of pressure dressings. The problem proved more difficult than anticipated for him and a little more than a year ago Dr. Wight joined to help him. Dr. Vilain returned to France three months later and Dr. Wight has continued with the observations. They are not yet completed to her satisfaction and it is hoped that during this next six months she will be able to devote additional time to complete them.

The observations may be tentatively summarized as follows. It is probable that a properly applied pressure dressing or a tight fitting plaster cast does diminish the loss of fluid from the plasma into the burn wound. The decrease in loss is slight, however, and therefore the experimental method needed to measure it has to be refined.

From the point of view of the clinical therapy of the burned patient it can probably be said that proper pressure dressings applied to burns of the extremities and the head do diminish slightly the volume of replacement therapy needed in the prevention or treatment of burn shock. The volume spared is slight and not too much is being sacrificed in the fluid therapy of the patient when the burn wound is treated by the open method. This is certainly true when adequate supplies of plasma or a plasma expander are available for the therapy and when the veins available are adequate.

C. Intermediary Metabolism.

The program of investigation of the changes in intermediary metabolism resulting from trauma has moved on a phase but continues to occupy a principal portion of our investigative efforts. (See Cope, Nardi, Quijano, Rovit, Stanbury and Wight, Ann. Surg. 137:165,1953.) We believe we have traced the function of the thyroid gland in response to burn trauma as accurately as we need to at the present time. We are examining thyroid function therefore in patients with severe fractures. We are still puzzling over the flood tide of the eosinophils found in the burned patient. Drs. Nathanson and Engel are carrying out further analyses of urinary steroid hormones, and Dr. Nardi is in full swing in his work on the nitrogen metabolism.

1. The Meaning of the Flood Tide of the Eosinophils in the Severely Burned Patient. In the report of a year ago we described the varying course of the eosinophil level in the blood following a burn injury emphasizing the prognostic significance of a continued low eosinophil count and the flood tide of eosinophils in the severely damaged patient responding well to his trauma. This work was subsequently written up and is published; the reprints were forwarded as technical reports during the period covered by this semi-annual report.

The published report describes 9 patients with continued low eosinophil counts who died as a consequence of their burn injury. We felt reasonably certain of our findings in that group. In the group with the flood tide of eosinophils later during the course of the grafting and healing of their wounds, there were only 5 patients. The range of eosinophils was considerable and we felt that further observations were indicated, first to substantiate the flood tide as a phenomenon and second to find out its meaning.

Accordingly we have continued to observe the eosinophil level of the blood in severely burned patients. We can report that the flood tide is indeed a phenomenon frequently encountered in the severely burned. We enclose a chart of a case encountered in these last 6 months. (See page 13 A.) The clinical course of this patient is described in the legend. An article has also appeared by Dr. Sevitt, from the Medical Research Council Burns Unit in Birmingham, England, describing the identical phenomenon. His article appeared while we were assembling our own data. Unfortunately we were not aware of the article and therefore did not refer to his work in our report.

Our interest has extended beyond confirmation to try to find out the meaning of the flood tide. We have been able to find that the elevated eosinophil count is still suppressed by cortisone or ACTH. It therefore remains under potential control of the adrenal gland. The flood tide is present throughout a period when Drs. Nathanson and Engel are able to demonstrate abnormally large quantities of the corticoids in the urine. The flood tide occurs therefore presumably when the adrenal is still hyperactive. Some other influence has become dominant. In considering the possibilities it seems logical to us to believe that the flood tide is related to the infection. Because the patient is doing well during the flood tide it represents a good omen and perhaps is related to a good immune body response

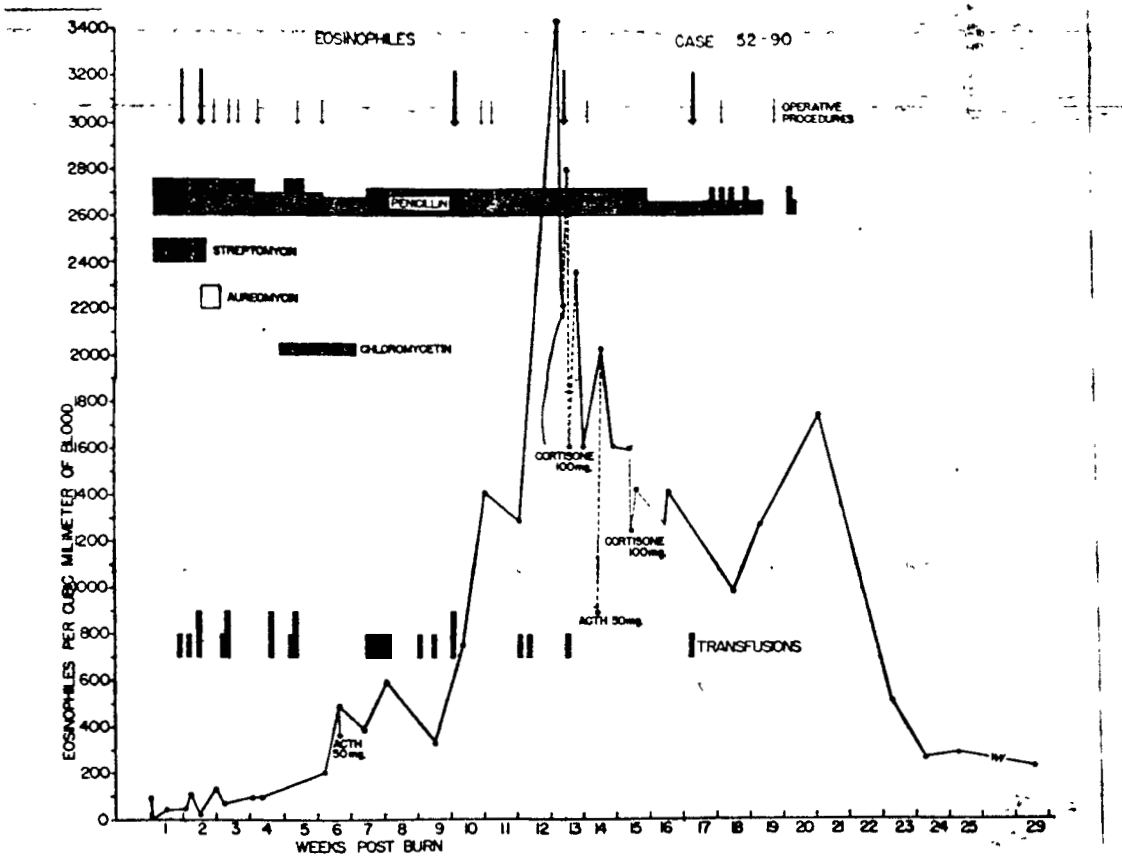

CHART ILLUSTRATING THE COURSE OF THE BLOOD EOSINOPHILES IN A PATIENT WITH DEEP BURNS OF MODERATE EXTENT. A 26 year old white male suffered a 20% third degree burn involving the entire circumference of both legs from the ankles to above the knees. The eisinophiles fell to almost zero shortly after the trauma. Excision and grafting of the burned areas was carried out on the sixth and eleventh days, and the patient responded well in the early period with initial take of the grafts. Supportive therapy included several whole blood transfusions. Gradually the grafts melted, apparently due to infection, and his condition deteriorated through the sixth week. There was only a moderate rise in his eosinophile count. In the seventh week he was given a daily transfusion for five days with marked improvement in his appearance and with cleaning up of the denuded areas. The third major operative procedure was carried out in the tenth week as his eosinophiles were rising at a rapid rate. From this date he did well clinically although a long time was required to clear up the infection of the burned areas and get them covered with skin. After reaching the peak of 3334 eos/cu. mm. in the thirteenth week, the count slowly fell as the patient improved, until it reached the normal level in the twenty-fourth week when he was nearly ready to go home. ACTH and oral cortisone given during the flood tide were followed by a significant drop in the eosinophile level.

of the patient to the infecting organism. We have no factual evidence to support this concept -- only armchair reasoning.

2. Pattern of Urinary Steroids -- Drs. Engel and Nathanson. Drs. Lewis Engel and Ira Nathanson have continued their studies of the urinary steroid excretion in collaboration with us. The emphasis in the past six months has been in patients with adrenal cortical disease. Four patients with the Cushing's type of adrenal cortical disease and two with adrenal cortical virilism have been studied both before and after operation upon the adrenal glands with reduction in adreno-cortical activity. It is believed that the findings in these patients will prove an interesting contrast to the steroid pattern of the burned patient. In addition four patients have been studied before and after total adrenalectomy for metastatic carcinoma of the breast. A comparison of the various clinical states associated with changes in adrenal cortical function should throw some light on the pattern of adrenal overactivity following burn trauma.

3. Intermediary Nitrogen Metabolism -- Dr. Nardi. This part of our program has become a dominant and exciting issue. Dr. Nardi has discovered a break in the wall of mystery enclosing the upset in nitrogen metabolism which follows burn trauma and he is pressing through the break as fast as possible.

The background of this project was given in the last semi-annual progress report. In brief, Drs. Nathanson and Hilda Wilson, while checking the completeness of 24 hour urine collections in our burned patients, analyzed the urine for creatine as well as creatinine. They found that the burned patients excreted large quantities of creatine, indicating an important derangement in nitrogen metabolism.

Dr. Nardi has extended the finding of creatinuria into a wider analysis of the excretion pattern of all the nitrogen. He has found an outpouring of a large quantity of amino acids. The excretion of the non-essential amino acids normally

present is increased. There are in addition other non-essential and essential amino acids put out in large quantities. The excretion of both non-essential and essential amino acids is larger than would be expected from the increase in total nitrogen. Therefore the amino acid concentration is abnormally great. In addition Dr. Nardi has studied the excretion pattern of the amino acids in patients with Cushing's disease and in patients before and after a variety of major operations. In the patients with Cushing's disease there is also an outpouring of a variety of amino acids which disappears after subtotal adrenalectomy. Following various operations the excretion is increased qualitatively and quantitatively. The variety and amount of amino acids is proportional to the magnitude of the surgery. In this latter group at least he suspects that the findings are the result of the failure of tubular resorption.

The aminoaciduria in burned patients and in Cushing's disease and that following surgery have already been written up and the manuscripts submitted for publication. A copy of the manuscript of each article is appended as Appendix C and D respectively.

These are exciting findings. They have led Dr. Nardi on to a study of the total nitrogen partition, for we feel that such a study will yield important information regarding the upset in nitrogen metabolism which follows trauma and the role the adrenal cortex may play in it.

Amino acid metabolism in the burned patient and in the patient with Cushing's disease is being further studied by Dr. Nardi using S^{35} tagged amino acid. The tagged acid is injected into the patient and its disposition in the body fluids and urine measured. Here again it is hoped to determine the role of the adrenal cortex in nitrogen metabolism in general and following trauma in particular.

D. Infection.

The only work in the field of infection carried on during this six month period has been the continued cataloguing of the bacterial organisms infecting burn wounds. Infection remains a major problem of the extensively burned patient and is still in our impression the major cause of death of the burned patient. Modern antibiotic therapy still does not answer the problem of bacterial organisms in a patient whose skin surface is half denuded. Better or more judicious use of the antibacterial agents now available would help, but our hunch is that immunologic considerations are more important. Knowledge of immune body production is needed. In the meantime nutritional and metabolic support is the best that we can offer.

No one in our group has the special knowledge of bacteriology and immunology which is needed to tackle this problem. The responsible investigator is about to visit Great Britain to study the Burn Units in Birmingham and Edinburgh and bacteriologists elsewhere, hoping to learn that promising leads in this field have been found.

E. Acute Dehydration and Metabolic Derangement Following Perforation of a Peptic Ulcer.

The metabolic derangements following operation have recently been much studied and much discussed. For the most part conclusions have been drawn from observations made in single cases or in just a few cases of a heterogeneous group of surgical procedures. Only in a few areas, such as burns and fractures, has a single entity been studied repeatedly, and in both of these extensively investigated conditions the variations within the group are wide. The experience to date with the metabolic changes in surgical disease might thus be called an horizontal one. Four years ago it occurred to us that it would be valuable to gather a more vertical understanding, studying one entity sufficiently often to encounter most of the variables. In this way we could hope to describe with authority any pattern which emerged.

The basic requirement for selection of the surgical condition to be studied was that it should be a disease entity with a relatively uniform pattern of injury from patient to patient. The consequences of the perforation of a peptic ulcer fulfilled that requirement and included the advantage of a clearly recognizable time of onset.

Three other factors also entered into our selection of perforated ulcers: the active controversy as to management of the perforation, the high mortality rate irrespective of the therapy chosen, and the probable similarity of the injury to that of a cutaneous burn.

Because the problem of therapy cannot be settled by mortality statistics and because of the continued high mortality, it is evident that further investigation into the factors contributing to the deterioration of the perforated ulcer patient is needed. Some of the confusion about the choice of therapy might be dissipated if we were to know more about the metabolic derangements and nutritional deficits which perforation sets in progress. Our selection of ulcer perforation for study was based in part on the hope that our findings might not only be informative regarding injury and operation in general, but that they might lead directly to improvement in the management of the ulcer patients and those with other intestinal injuries and perforations.

The perforation itself is a wound of minor importance. It is the insult of peritoneal contamination with gastric juices which constitutes the real injury, a chemical burn. The area of the peritoneal surface involved is probably wide enough to be equivalent to a skin burn of moderate extent. This comparison with a cutaneous burn is an obvious one and suggested the probability that the same methods of study which had contributed so much to the understanding of burn shock might yield valuable information about the effects of peptic ulcer perforation and any subsequent operation as well.

To insure an adequate view of the pattern of injury and its complications the study has included 24 patients. There was no selection of cases. The patients were consecutive in so far as the Surgical Metabolic Unit and Laboratory were able to accept patients for study. Treatment included simple operative closure in 23 cases. There were no primary resections. Twenty of the patients ran relatively uncomplicated courses. Four required secondary operations. One patient was managed conservatively without operation. There were no deaths. Chance dictated that all the patients should be males.

The observations have been completed and are currently being written up. The manuscripts unfortunately are not ready for inclusion with this report; they will be submitted subsequently.

The study has been rewarding. The chemical injury is followed by an acute dehydration in many ways like that following a burn and is equivalent in degree to that of a burn of 20 to 30% of the skin surface.

There are curious differences, however. The potassium level of the blood, for example, falls if no parenteral potassium is given. This is not encountered following a cutaneous burn. The K:N ratio in the urine is the reverse from that in the burned patient, there being a relatively greater potassium than nitrogen excretion following ulcer perforation.

A pattern did emerge. An improved scheme of therapy has evolved.

Part III. Bibliography

A. Articles published and reprints submitted during the period of this report:

1. Quinby, W. C., Jr., and Cope, O.: Blood Viscosity and the Whole Blood Therapy of Burns. Surgery 32:316,1952.

2. Wight, A., Raker, J. W., Merrington, W. R., and Cope, O.: The Ebb and Flood of the Eosinophils in the Burned Patient and Their Use in the Clinical Management. Ann. Surg. 137:165,1953.

3. Cope, O., Nardi, G. L., Quijano, M., Rovit, R. L., Stanbury, J. B., and Wight, A.: Metabolic Rate and Thyroid Function Following Acute Thermal Trauma in Man. Ann. Surg. 137:165,1953.

B. Manuscripts in press or submitted for publication.

1. Raker, J. W., and Rovit, R. L.: The Acute Red Blood Cell Destruction Following Severe Thermal Trauma in Dogs; Based on the Use of Radioactive Chromate Tagged Red Blood Cells. Submitted for publication to Surg., Gyn. and Obstet. Manuscript appended as Appendix A.
2. Nardi, G. L.: The Escape of "Essential" and "Non Essential" Amino Acids in the Urine of Severely Burned Patients. Submitted for publication to J. Clin. Invest. Manuscript appended as Appendix C.
3. Nardi, George L. Urinary Loss of Amino Acids after Surgery. Submitted for publication to Surgery. Manuscript appended as Appendix D.
4. Nardi, George L. Radiocative Measurement of Proteolytic Activity. Submitted for publication to Science. Manuscript appended as Appendix E.

C. Manuscripts in preparation.

1. Cope, O., and Raker, J. W.: Cushing's Disease: The Surgical Experience in Treating 43 Cases.
2. Wight, A., Hopkirk, J. F., and Cope, O.: The Physiologic Derangements and Deficits Imperilling the Patient With a Perforated Peptic Ulcer. I. The Dehydration and Fluid Shifts.
3. Wight, A., Hopkirk, J. F., and Cope, O.: The Physiologic Derangements and Deficits Imperilling the Patient With a Perforated Peptic Ulcer. II. The Electrolyte Imbalances.
4. Wight, A., Hopkirk, J. F., and Cope, O.: The Physiologic Derangements and Deficits Imperilling the Patient With a Perforated Peptic Ulcer. III. The Nitrogen Depletion.

Part IV. Personnel

The following members of the staff have continued to serve throughout the time of this report.

Responsible Investigator	Oliver Cope
Principal Investigators	Bradford Cannon George L. Nardi Anne Wight
Clinical and Research Fellow	Charles L. Minor

Dr. Baker, a Principal Investigator for the past three years, has now been promoted by the Harvard Medical School to Faculty status as Associate in Surgery. He is now established as an independent member of the Department of Surgery. He has applied for and received a Grant from the United States Public Health Service to continue his studies on intracellular electrolytes. He is continuing to share in certain activities of this Task Order and will continue to use in collaboration some of the instruments. He will receive no further salary under this contract.

Dr. Nardi has taken Dr. Baker's place as Laboratory Administrator. It is anticipated that he too will be promoted to Faculty status in the next two to three years and will also receive separate support.

Dr. George S. Bascom joins the project as Clinical and Research Fellow for the year starting 1 July 1953. He has been granted a Public Health Service Research Fellowship for the year. He graduated from the Harvard Medical School in 1952 and has served his surgical internship at the New Haven Hospital as the first rung in his surgical training. After the year in investigation with us he returns to the New Haven Hospital to continue with the residency training. Dr. Bascom has long had an interest in investigation and has participated in research programs while a student and an intern.

Dr. William C. Quinby, Jr., has not been able to find the time to return to

work part time on this project. This is greatly regretted.

On the technical staff, our half time bacteriologist, Mrs. Cummins, leaves us as of the 20th of June. Her husband, a physician, has moved to Illinois. Mrs.Lois Shea, a chemical technician, was forced to withdraw because of pregnancy, and her place has been taken by Mr. O'Brien, a college graduate who is working his way through a night law school.