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FINAL REPORT

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TITLE OF STUDY:	Thermal and Radiation Injury
PERIOD COVERED:	1 July 1949 - 31 May 1959
INVESTIGATORS:	Everett I. Evans, M.D. (1 July 1949 - 14 January 1954) B. W. Haynes, Jr., M.D. (14 January 1954 - 31 May 1959)
INSTITUTION:	Medical College of Virginia Richmond, Virginia
CONTRACT NO.:	DA-49-007-MD-99
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ABSTRACT

1. Preparing Institution: Medical College of Virginia
Richmond, Virginia

2. Title of Report: Thermal and Radiation Injury

3. Principal Investigators: Everett I. Evans, M.D. (1 July 1949 - 14 Jan. 1954)
B. W. Haynes, Jr., M.D. (14 Jan. 1954 - 31 May 1959)

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This contract was initiated in July 1949, to investigate thermal and radiation injury. Accomplishments included (1) development of the Evans' Formula for estimation of fluid requirements following thermal injury, (2) development of a universal dressing for burns, (3) elaboration of the syndrome of pseudodiabetes of stress, (4) delineation of the effects of burn injury plus total body radiation, (5) comprehensive studies showing the cause of the anemia of thermal burns, (6) characterization of the light energy required to produce different depths of flash burn in human volunteers, (7) observations on the adrenocortical response to thermal injury, (8) observations on the adreno-medullary response to thermal injury, characterizing a syndrome of adreno-medullary insufficiency, and (9) studies of the nutritional requirements of severe burns according to age and sex. Annual reports, publications and final report are available.

NOTE: Copies of this report are filed with the Armed Services Technical Information Agency, Arlington Hall Station, Arlington 12, Virginia, and may be obtained from that agency by qualified investigators working under Government contract.

Contract DA-49-007-MD-99 was initiated on 1 July 1959, with Dr. Everett I. Evans as Principal Investigator. This event marked the beginning of an investigative program in burns, resulting in the establishment of a clinical burns unit and extensive laboratories used to investigate various ramifications of the burn problem. Following Dr. Evans untimely death in January 1954, I assumed the responsible investigatorship and continued this until the contract termination. Summarization of approximately 10 years' work of many people and one million dollars expenditure is not an easy task. The areas of interest of those working under this project are listed under personnel. Detailed annual reports have been filed and cover the majority of the work done under this contract. The following commentary is a summary in sequence as the work unfolded.

During the period 1 July 1949 through 31 December 1950, the project was departmentalized and effort directed in 3 directions.

1. The development of a biophysics group.
2. An experimental surgery group.
3. Clinical burn surgery group.

The biophysics division concentrated upon calibrating a one million volt beryllium window x-ray tube to be used in studies on thermal and radiation injury in the dog. The experimental surgery group concentrated on developing a standard and uniform thermal injury preparation in the dog, and, after this, the measurement of the quantity of plasma lost following a given degree of injury with relation to time. The combination

of a standard thermal injury plus total body radiation in quantities varying from 25r to 100r was also studied and the mortality of additional total body irradiation to the standard burn observed. Preliminary observations suggested that beta hemolytic streptococcal septicemia was the basic cause of the increased mortality associated with a reduction in white blood count due to irradiation. During this period the clinical burn surgery group set to work studying the possible use of the data gathered in the experimental animal on the amount of fluid required to treat the severely burned patient. Having noted that the experimental animal lost approximately 1cc of plasma per kg. of body weight per per cent burn, the Evans' Formula was devised with this as a baseline and applied to the burn patient. Early studies suggested that 1cc of colloid per kg. body weight per per cent burn, an identical amount of saline solution, and 2000cc of 5% dextrose in water were approximately the quantity of fluid required to treat the severely burned patient well during the first 24 hours. One-half of this quantity, excepting the 2000cc water requirement, was required during the second 24 hour period following injury. This formula has since been extensively tried and forms a therapeutic standard through the world.

Initial studies using Swedish dextran for the treatment of burn shock were encouraging, suggesting that this substance is a safe and effective plasma substitute, that its use is followed by a good urinary output, and no adverse effects on liver or kidney were noted.

Recognizing that the closed dressing principal forms a basic concept for the treatment of the burn wound and that materials commonly

present in the hospital are difficult to fashion into a large burn dressing, a universal protective dressing was developed which was subsequently made by Johnson and Johnson Company and has been since stock piled by the Armed Services and Federal Civil Defense Agencies for emergency use. We continue to use these dressings today and they are well designed for the purpose and meet a real need.

Early studies on anemia following thermal injury were instituted during this period and measurements of urine and fecal urobilinogen indicated that hemolysis was a significant factor in the anemia of burns. Recognizing the importance of N-15 tagged hemoglobin as a tool for studying the anemia of thermal injury, a Nier type mass spectrometer was put into operation by the biophysics division and initial studies of the break-down of hemoglobin evaluated by N-15 stabile isotope tagging were carried out. During this period studies of the stress response and adrenocortical function were carried out serving as a background for the evaluation of the use of ACTH and cortisone clinically in the severely burned patient as well as following homograft application.

During 1951-52 the clinical burns unit expanded into one 16 bed ward and one 7 bed ward, thus improving the facilities for treating such patients. During this period 80 severely burned patients were treated with dextran of various origins including Swedish, British and American. Thirty-six of this number were treated with dextran exclusively as regards colloid administration. In summary, these patients responded nicely to this treatment and no allergic or other reactions were observed. The

clinical impression was that this material is as effective as plasma in the management of burn shock in most patients.

During this period the use of N-15 tagged red cells progressed and it was observed that there was a marked reduction in hemoglobin synthesis following burn injury in the dog. Those red cells produced after burn injury appeared to have a normal life span. A similar study was completed in one patient.

During this period a bacteriology unit was established in order to study the flora of the burn wound. 82 patients were evaluated during that year. A tentative conclusion following the year's study was that presently available antibiotics, although they seemed to diminish the severity of invasive infection, by no means solved the problem of burn wound infection.

Extensive study of the stress response to thermal injury was made in 21 severely burned patients. Results indicated that the quantitative eosinophile count reflects quite well the adrenocortical function of the burn patients. Depression of eosinophile count was greatest and longest in large burns, least in small burns, and quantitative balance studies of urinary nitrogen and studies of sodium, potassium and urinary corticoids confirmed this conclusion. Clinical trials of ACTH and cortisone in the shock phase of severely burned patients lead to the conclusion that this form of therapy could not be expected to provide much gain in survival in the extensively burned patient. Pseudo-diabetes similar to that found in Cushing's disease was discovered in 11 severely burned patients

who had received a high carbohydrate, high caloric food intake soon after burn injury. Reduction of the level of carbohydrate intake appeared to decrease the incidence of this complication.

In an effort to determine the nutritional requirement of the burn patient, 50 patients were studied metabolically during this year. The diets used were almost entirely liquid and it was concluded that the dietary requirements of the severely injured patient are considerably higher than normal, although the amount was not determined. It was observed in this connection that a planned program of exercise in bed greatly reduced the negative nitrogen balance in the traumatized individual.

Dogs were given the standard 20% body surface area contact injury combined with 100r total body irradiation. This combination of injuries resulted in the mortality of 73% in contrast to a mortality of 12% from the burn alone. All dogs dying as a result of the combined injury had a blood stream infection of beta hemolytic streptococci. When this same experiment was repeated treating the animals with penicillin, the mortality dropped to approximately 18% and no animal developed a blood stream infection. During this year the biophysics team participated in Operation Ranger and Operation Buster and expended considerable effort in developing a means of giving a flash burn to animals or human volunteers using an army search light.

Following the untimely death of Dr. Everett I. Evans on 14 January 1954, the project continued along the lines that he had set up in some respects and shifted emphasis in others. Gross mortality in the

burns unit remained approximately the same as in previous years, that is, 16%. Hemografts were employed in burns over 40% in five instances during this year with excellent results. An evaluation of colloid therapy during the year indicated that the Evans' Formula was quite accurate in predicting the extent of fluid required in treating the severely burned patient. It was observed that with burns of approximately 20% body surface area, plasma substitutes alone substituting for the colloid requirement were adequate, whereas with burns of larger extent, and especially with extensive third degree destruction, whole blood was required in addition.

Early studies of adrenalin and nor-adrenalin excretion in the urine suggested that both of these hormones rise to high levels shortly after injury and gradually return to normal levels about 3 weeks post-burn. During the year, studies of the red cell mass measured by cromium 51 tagged red cells were carried out. Losses up to 30% of the total red cell mass were demonstrated four days following injury. In general, burns of less than 30% body surface area demonstrated from 15% to 20% reduction in red cell mass by the second or third day after injury. In burns of 30% or more, 25 to 30% red cell loss was demonstrated by the end of the third to the fifth day. A second approach to the problem of the anemia of thermal burn was carried on, utilizing N-15 tagged hemoglobin. N-15 tagged erythrocytes from a donor fed N-15 tagged glycine were transfused into a patient with 15% third degree burn. The break-down with erythrocytes tagged with this material was then followed in the blood and in the fecal stercobilin. Data from the N-15 tagged hemin in the circulating blood and

stercobilin in the stool suggested a slightly shortened life span of the erythrocytes in this particular patient. Further studies were planned to determine if this was a true finding or an individual variation.

During the year, flash burn studies on 44 white volunteers and 20 negro volunteers were carried out to determine the dosage range of a light source necessary to produce different depths of thermal injury. As a result of these studies it was determined that 2 calories per sq. cm. of light energy are required to produce a first degree burn, 3.2 calories per sq. cm. a superficial second degree burn, 3.9 calories per sq. cm. a well defined second degree burn, and 4.8 calories per sq. cm. a deep second degree or possibly third degree burn. In the experimental laboratory, studies were continued utilizing total body irradiation of 100r plus a standard hemorrhage and a standard trauma such as a small bowel resection. This combination of injuries did not appear to increase the mortality observed following the 20% burn. During this period, extensive burn wound cultures were carried out revealing a combination of organisms present which showed considerable resistance to aureomycin which had been used topically. It is also observed that the use of the Colebrook dressing room was associated with a low incidence of airborne cultures between dressings, suggesting that the low incidence of beta hemolytic streptococcal infection could be attributed in part to the use of this facility.

In order to evaluate the adreno-cortical response to burn injury, a study of 17 hydroxycorticosteroids in plasma was carried out, using the Nelson Samuels chromatographic method. Early results indicated

a marked response following burn injury.

Nutritional studies using the nitrogen balance technique were continued during the year. A few patients receiving 4 grams of protein per kg. and 45 calories per kg. demonstrated early recovery of positive nitrogen balance and satisfactory clinical progress. Whether this represents an optimal intake remained to be seen, and further studies were continued.

During the year 1954-55 the gross mortality in the burn unit continued at 15%. Continuing the evaluation of colloid therapy and extending the series to 158 cases, it was observed that these patients required 1.46cc per kg. per per cent burn compared to the Evans' Formula estimate of 1.5cc per kg. per per cent burn. It was observed that children required proportionately more colloid than adults, the average being 1.75cc per kg. per per cent burn during the first 48 hours. Comparison of the open and closed method of treatment during this period pointed out superiority of both methods when properly applied. One additional indication for exposure treatment was delineated, that is, the massive burn above 50% body surface area. The problem of hyperpyrexia in such an injury if any significant part of the body is dressed is so great as to contraindicate the use of the closed method except for the arms and hands. In attacking the problem of early removal of burn slough, the use of dressings with surgical debridement, massive surgical excision with immediate homograft, enzymatic debridement, and mechanical removal of slough by rotary brush were all tried with variable results. In most instances the use of weekly dressings

with local debridement seems superior. An occasional patient who has a limited area of third degree burn may benefit by surgical excision and immediate or delayed grafting.

During this year, an IBM record system was inaugurated for documenting the changes seen in the severely burned patient. This was extended to the patients admitted from the inception of the burn unit in 1949 and planned to continue in order to give a large volume of clinical material for statistical evaluation.

Continued studies of urinary excretion of adrenalin and nor-adrenalin demonstrated that certain patients who recovered from their injury show a pattern of initial high adrenalin nor-adrenalin output gradually returned to normal levels over a 3 week time. Certain patients dying as a result of their injury demonstrated elevated adrenalin nor-adrenalin output in the urine. There were a few patients who demonstrated sharp fall in urinary output of adrenalin and nor-adrenalin prior to death. In this group a syndrome of adrenal medullary insufficiency was suggested.

Continuing the study of anemia of thermal injury, another patient was treated with N-15 tagged hemoglobin and the breakdown of these cells studied in the blood and in the stool. On the basis of the studies in this patient, there did not appear to be any significant shortening of mean erythrocyte survival of cells transfused into the severely burned patient.

In the experimental laboratory, it was undertaken to produce flash burns of the retina of the rabbit in an effort to gain information about the energy required to do this. A search light formerly used to produce

skin burns was attached to an optical system to produce burns of the rabbit retina.

Studies on the adrenal response of severely burned patients were continued. Twelve patients were studied with third degree burns ranging from 8 to 46% body surface. Patients who recovered from their injury showed a good reactivity on the day of burn and the day following the burn and reached normal corticosteroid levels on the fourth day post-burn. Patients who died in the first and second week after severe injury often showed low plasma levels on the day of burn due to shock and poor general condition and reached their highest level on the day following burn when shock had subsided. They often had elevated plasma levels well outside the normal range after the fourth post-burn day. Very high plasma levels of 17 hydroxycorticosteroids above 50 micrograms per cent on the fourth post-burn day appear to indicate a poor prognosis.

During the year 1955-1956, there were 158 admissions to the burn service with an overall mortality rate of 22.1%. Though this figure was somewhat in excess of that of former years, an increased average age and increased per cent burn accounted for the difference. It was observed in the previous year that there was good agreement between the predicted colloid requirement according to the Evans' Formula and that actually delivered. During this year evaluation of 63 patients with regard to saline requirements were carried out. Though there was considerable individual variation, the average quantity given was 1.36cc per kg. per per cent burn as compared to the anticipated formula requirement of 1.5cc

per kg. per per cent burn. Associated with this treatment, serum sodium and chloride levels remained relatively normal and treatment was in general satisfactory.

Further use of skin homografts made it clear that their greatest utilization was in the patient with 40 to 50% burn who was able to remove his dead tissue, achieving a clean granulating wound but was not in sufficiently good condition to withstand surgery and anesthesia.

During this year the management of third degree burns involving bone came under consideration, and a plan of treatment was evolved which gave good results. In the case of the third degree burn over the tibia the surrounding area was excised or debrided and a clean granulating wound obtained. This area was then grafted with split-thickness skin grafts. Following wound healing the dry eschar overlying the tibia was then excised and portions of the cortex of the tibia excised until healthy cortical bone was obtained. At this point, following hemostasis, split-thickness grafts were then placed directly over the exposed tibia. Skin growth was good and functional use has been satisfactory. Shin guards are worn for a time until the patient accommodates to his situation. In no patient has it been necessary to perform a pedicle graft.

Further studies of the urinary excretion of adrenalin and nor-adrenalin were carried out and 14 patients evaluated. In general, the patients appear to fall into the following groups:

1. Those patients who recovered from their injury showed an initial rise in adrenalin and nor-adrenalin output in the urine which gradually

returned to normal levels over a period of 2 weeks to 3 months.

2. Those patients who die from their injury at which time there is marked elevation of adrenalin and nor-adrenalin in the urine.

3. Those patients who die with normal or low levels of adrenalin in the urine and increased quantities of nor-adrenalin.

Studies of the survival of N-15 labelled erythrocytes were continued. In previous years studies of the survival of such erythrocytes in patients with third degree burns of approximately 15 to 20% were carried out. In two instances the infused cells were administered at 10 days and 40 days post-burn. In this study, using the same techniques, N-15 labelled erythrocytes were infused 12 hours after the burn. Data from this study suggests that the burn patient preferentially destroys her own erythrocytes in the first 10 days following the burn. Following this, the transfused erythrocytes disappear at a rate similar to that of the patient cells, suggesting that the life span of the infused erythrocytes is approximately the same as the life span of the donor erythrocytes in the donor. These data suggest that the anemia of thermal burn is due primarily to cells damaged at the time of injury.

When N-15 tagged glycine is fed to a donor, it not only labels heme but also labels plasma protein. A series of half life studies of plasma protein in the donor men were carried out since the opportunity was presented and there was a paucity of data on the point in the literature. Studies of the disappearance curve of plasma protein in the 4 donor males demonstrate that the half life of total plasma protein is 7 to 8 days. This is in

agreement with the few published studies on the subject.

In connection with the N-15 tagged red cell study which demonstrated interference with normal life span of cells following thermal injury, studies of the P-32 uptake were carried out. Human erythrocytes were heated in vitro for 3 minutes at temperatures ranging from 48 to 55 degrees centigrade. These studies indicated that the phosphate uptake and glycolytic activity are closely related in heated red cells and that heat interferes with this energy producing mechanism. To determine if 200r x-irradiation of whole blood had any effect on the red cell P-32 uptake, 3 experiments with human blood and 3 with dog blood were carried out. No effect on P-32 uptake was noted 17 and 24 hours post-irradiation. To determine if systemic disease affects energy producing mechanisms in the red cell as evidenced by P-32 uptake, a series of patients suffering from rheumatic arthritis, disseminated lupus erythematosus, Whipples Disease, and tuberculous pericarditis were studied. No change from normal was observed.

During the year, bacitracin, neomycin, and polymyxin were applied to burn wounds, in powder form, in an effort to determine the effectiveness of this approach to treatment. This combination consistently failed to eliminate sensitive organisms. The effectiveness of these three agents in an ointment base was planned for evaluation.

Evaluation of septicemia as the cause of death was begun actively and the establishment of culture methods identical with those used at the surgical research unit at Brooke Army Hospital. During the year, 20 blood cultures were drawn on a series of 15 patients. There was one

positive blood culture in the group for a group D enterococcus and pseudomonas aeruginosa. Further data were sought.

As a part of a study of the metabolic effects of burns, the P-32 uptake after intra-peritoneal injection of radio phosphorus was determined in different areas of the brain and other tissues in the body, including the pineal gland, the anterior and posterior lobe of the pituitary, the adrenal cortex and the medulla of the adult male rat. The most striking finding was the marked fall in relative specific activity of the pineal gland 4-1/2 hours after the burn. This depression was short lasting with the values at 17 and 48 hours approaching normal. In contrast, the adrenal cortex showed approximately normal levels at 4-1/2 hours post-burn but with some decrease at 17 and 48 hours. The differences, however, were slight. These studies suggest that the pineal gland is not likely to be a functionless, vestigial organ in the adult rat.

During this year, the series of patients with severe burns studied with regard to plasma hydroxycorticosteroids was extended to 31 patients ranging from 12 to 100% body surface area of burn. Twenty-two of these died as a direct result of the burn. These studies permit the following conclusions:

1. The patients who recovered from their burn showed the expected rise in plasma 17 hydroxycorticosteroids on the day of burn and on the following 2 to 4 days.

2. The patients that died as a direct result of their burn showed good adrenocortical reactivity as judged from their plasma levels on day 0

and day 1. However, following this the levels of corticosteroids were rather consistently above the normal range on day 4 in contrast to the previous group. It was also characteristic that the patients who died had an elevated level on the day of death.

It is a frequent observation that burn injury produces an alteration in the albumin globulin ratio with a decrease in albumin and an increase in globulin. During this year a study of the seromucoids representing hexose-hexosamine rich alpha globulin, chiefly alpha 2 globulins, were carried out in 19 patients. There appeared to be a good correlation between the amount of tissue destruction and the increase in seromucoids. A rapid rise occurred on the day of injury and on day 1, usually followed by levelling off in the second week in the patients who were recovering. High serum levels were noted in the patients who died. After the burns healed, seromucoid concentrations quickly reverted to normal values before the A/G ratios did so. In an effort to characterize the protein change in more detail, 17 patients were studied with regard to the electrophoretic pattern of the serum protein. As previously indicated, the early rise in alpha 2 and alpha 1 globulins represented the increase in seromucoids. There was a later rise in gamma globulins presumably related to antibody formation.

Studies of the nutritional problem in the severely burned patient continued during the year with the addition of 26 patients. With the addition of these studies, certain conclusions are permitted. Severely burned children can be maintained in good nutritional condition when given dietary intakes of from 1 to 1-1/2 times their normal requirements. Extremely

severely burned child may require as much as twice normal. Severely burned women have been kept in good nutritional state by supplying them with 1-1/2 times their normal requirements with regard to caloric intake and from 2 to 4 times their normal protein requirements. Young adult males on a dietary intake similar to females will show greater nitrogen losses for comparable injury. The optimum intake for the severely burned male is not clear but would seem to be in excess of that for the female.

During the remaining years studies proceeded along similar lines to those previously described. Hospital mortality for burn patients remained constant. In an effort to control possible toxic absorption from the burned area, hyperthermia was used in five severely burned patients in order to reduce body temperature, body metabolism, and decrease absorption from the skin area. In summary, the use of hyperthermia was associated with a reduction in pulse rate and is compatible with maintenance of excellent peripheral circulation and adequate urinary function. There appears to be some relationship between the rectal and the subcutaneous temperatures in such patients, though this is not direct and was quite variable in the cases studied. On the basis of past experience, hyperthermia from these patients did not significantly alter the anticipated clinical course.

By a continuing evaluation of the colloid requirements in severe burns, the applicability of the Evans' Formula as a general guide to replacement therapy was pointed out, the tendency of the formula to under-estimate the colloid requirements in the child clarified, and the usefulness of dextran as a plasma substitute established. In a recent report summarizing our

experience with the use of dextran in the treatment of burns, it was emphasized that this substance has been able to relieve the shock following burn injury, promote urinary output, and has been free of allergic or other reactions. Prolongation of bleeding time has been reported following the use of dextran in normal human volunteers. No bleeding tendencies were observed in an extensive case series where dextran was used clinically in severe burns and in a control series of studies utilizing 25 burn patients there were no significant abnormalities of bleeding time attributable to dextran.

One additional study of N-15 tagged erythrocytes in a severely burned patient was carried out. Having tagged hemoglobin with N-15 glycine in a donor, the cells were transfused into a recipient approximately 12 hours after injury. In summary, from fecal stercobilin data and hemin data, it is apparent that some factor operating in the recipient's body produced premature aging of the infused erythrocytes in contra-distinction to earlier studies. The nature of the process was unclear, though some alteration in biochemical function appears likely. The result was a premature breakdown of the transfused blood cells. Further investigation of the phenomenon of premature aging is clearly necessary in order to understand the anemia of thermal injury.

Monthly cultures of the nose and fingers of burn ward personnel were performed over a period of several years. It was found that the incidence of positive finger cultures for pathogens could be virtually eliminated by a thorough hand washing program. However, the nasal carrier

rate for coagulase positive staphylococci which varied up to 30% was found to be persistent with little change throughout the year. Phage typing of these nasal staphylococci does not tend to incriminate them as predominant sources for wound infection. Continued metabolic studies added an additional 18 patients to the series, bringing the total number of patients studied over the term of the contract to approximately 100 utilizable cases. In summary, it may be stated that children in general will respond well to 1 to 1-1/2 times their normal food requirement, that adult males and females do well on approximately 2 grams of protein per kg. of body weight per day and from 40 to 60 calories per kg. per day. It is planned to review these studies in detail and present them in monograph form since they are a unique collection of data.

Personnel

Division of Clinical Studies: Dr. Oliver J. Purnell, Dr. Paul Robinette, Dr. Mary Martin, Dr. Steffen Birkeland.

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