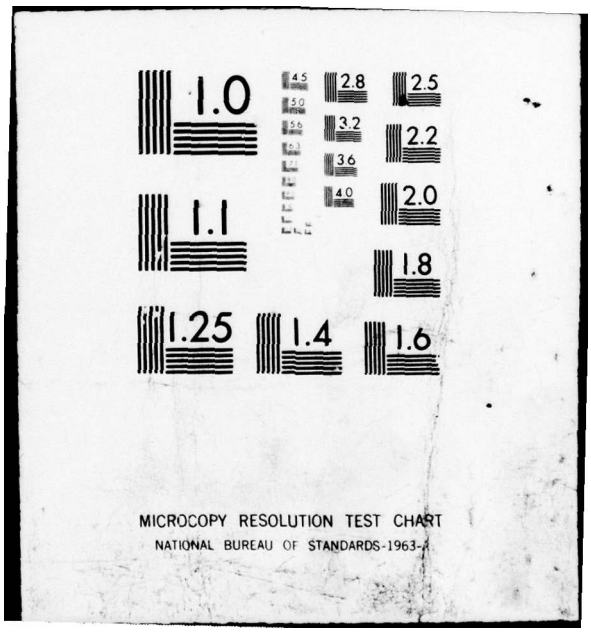
AD-A064 968 HARVARD MEDICAL SCHOOL BOSTON MASS DEPT OF SURGERY F/G 6/5
A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA.(U)
FEB 79 F D MOORE, N E O'CONNOR DADA17-73-C-3022

UNCLASSIFIED NL

1 OF 1
AD
A064968

END
DATE
FILMED
4-79
DDC


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0
5.6
MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

REPORT #1

# A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA



ANNUAL SUMMARY REPORT

Francis D. Moore, M.D.
and
Nicholas E. O'Connor, M.D.

February 1, 1977-January 31, 1978

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Washington, D.C. 20314

Contract No. DADA 17-73-C-3022

Department of Surgery
of
Harvard Medical School
Peter Bent Brigham Hospital
Boston, Massachusetts 02115

DADA-17-73-C-3022

ANNUAL REPORT - February 1, 1977 - January 31, 1978

# A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA

## I METABOLIC STUDIES

### Total Body Protein Turnover As Measured By $N^{15}$ Enriched Glycine

During the past two years this method has been established in our laboratories and our first set of normal volunteer control experiments have been completed. These data are about to be published and were recently presented at the Society for Surgical Research at Helsinki, Finland by Dr. Sim of our laboratories.

These normal control experiments turned out to be unexpectedly interesting. We had five subjects who served as their own control on three separate occasions.

On the first occasion a normal, oral diet was taken with zero balance. On the second occasion the run included the provision of nutriments solely as intravenous amino acids without any other substrate or oral nourishment. On the third occasion the same infusion was given but with added glucose in the amount of 450 gms. per day.

Each one of the "runs" were for 7 days, yielding a very stable period for metabolic study. The $N^{15}$ glycine technique was used by constant infusion over a 60-hour period at the close of each run.

The normal volunteer subjects, fasting, save for the measured intake indicated above, showed on normal diet a turnover of 3.4 gms. of protein/kg/day. Synthesis and catabolism were well balanced. On the intravenous regimens the turnover rate was markedly reduced to 2.6 gms. of protein/kg/day. This was associated with a reduction in synthesis and a normal level of catabolism as one would predict with a negative balance. With the added glucose there was a marked increase in synthesis which then balanced catabolism. This was a conclusive demonstration that when carbohydrate energy is added to amino acids there is an increased rate of protein synthesis than with amino acids alone.

Of unusual interest in this experiment was the demonstration that with intravenous intake the total body protein turnover or "Q" is reduced, as mentioned above. This reduction is interpreted as being due to a shutoff of pancreatic and gastrointestinal digestive enzyme synthesis. Without oral intake, the local secretory stimuli to the production of these enzymes are markedly reduced. The total weight of protein synthesized daily by these digestive glands and the pancreas may approximate 15-2- gms. This finding has not previously been reported and requires further work for additional interpretation.

When a nitrogen 15 enriched amino acid is infused and the degree of enrichment of urea in the urine measured, as with the $N^{15}$ glycine method, one must be strict in the interpretation of what is being measured. Local recycling of amino acids in and out of protein without deamination will not be measured by the method. There is no low molecular weight pool of nitrogen compounds that can compete with the huge dilution volume of total body protein synthesis to account for the turnover rates. The turnover rate or "Q", is therefore the independent variable measured by this technique and is the important single number coming out of the mathematical treatment of the urea enrichment. This mathematical reduction of the data is extremely simple, its simplicity depending upon the 60-hour infusion and the attainment of a plateau. The patient's own body is therefore, the "integrator" in the differential equation for isotope incorporation into synthesis. This is the beauty of this method as opposed to single pulse injections.

A weakness of the method, however, is that the differential measurement of synthesis and catabolism depends upon numerical input from the measured nitrogen intake and output. The deduction of synthesis and catabolism from $N^{15}$ glycine enrichment curves is therefore, not independent of the observed balance. This is important to emphasize, both in our work and in evaluating other work from the literature.

Effect Of Catabolic Hormones On Glucose Pools And Turnover

During the past two years, a series of experiments was carried out in which tritiated glucose was used as a tracer for measuring minimum glucose mass, glucose replacement rate and glucose space in man. A single injection of (2-$^{3}$H) glucose was used as the tracer. This method entails measuring a steady state distribution of the tracer, and then the amount of tritiated water that accumulates as the glucose is oxidized. This allows for an estimation of the rate of glucose oxidation, and the pool sizes.

Two sets of experiments were carried out with normal volunteer subjects. The first group of subjects was given infusions of glucagon, norepinephrine and then glucagon and norepinephrine combined, and the second group was given infusions of hydrocortisone and insulin. The effect of these hormone infusions then on minimum glucose mass, glucose replacement rate and glucose space were determined.

The results showed that when subjects were rendered hyperglycemic by glucagon, norepinephrine, and hydrocortisone infusion, minimum glucose mass and glucose turnover increased; the glucose space was unaffected. During insulin infusion glucose concentration fell significantly, minimum glucose mass fell to a lower degree, and the glucose replacement rate was increased sharply. There was an increase in the glucose space after insulin infusion suggesting that part of the fall in glucose concentration was due to the redistribution of the glucose in a larger space.

The interplay between hormones which raise or lower the serum concentration of glucose has long been recognized as a crucial factor in the control of glucose homeostasis. In these studies there was an elevation of the serum glucose concentration in response to infusions of glucagon with and without additional norepinephrine. There were also elevations of the serum glucose concentration with infusions of hydrocortisone. The addition of norepinephrine to glucagon infusion produced a more pronounced hyperglycemia. Glucagon alone and with norepinephrine also increased the glucose replacement rate. With glucagon, the hyperglycemia and increase in glucose replacement was a manifestation of a dynamic steady state establishing itself under the influence of this hormone.

Insulin alone on the other hand produced a hypoglycemia but with a sharp increase in glucose replacement rate. It is well known that a prime action of insulin is to enhance the transport of glucose across cell membranes, and part of the decrease in serum glucose concentration is to some degree caused by the redistribution of glucose throughout a larger space, and not necessarily wholly as a result of increased glucose utilization.

These studies demonstrate that changes in serum glucose concentration after hormone infusion are the result of a complex combination of alterations in glucose space and replacement rate. They help to explain the hyperglycemia seen following trauma and burns.

Amino Acid Infusions

The work in this laboratory on the utilization and metabolism of intravenous amino acids as the sole nutritional substate in fasting normal human subjects has been completed and published. In the normal human subject, many variables can be controlled; the achievement of an ideal body fuel economy is quite simple; if a favorable utilization of injected foodstuffs cannot be achieved in this setting, it is unlikely, and remains to be proven that utilization will be satisfactory under the challenges of acute surgical trauma. In this experimental model, employing four normal human volunteer subjects, nutrition was provided by the intravenous infusion of isotonic amino acids (freamine #2) at a 3.4% concentration. No other source of calories or nutrients was provided. In this setting utilization was poor; the subjects were in negative nitrogen balance throughout the infusion period. The nitrogen excretion was significantly greater than the total of infused nitrogen. The changes in protein fat and carbohydrate intermediates, as well as the alteration in hormone concentrations suggest the following endocrine governance of fuel economy in this setting: a sharp rise in glucagon with maintenance of insulin concentration; rapid gluconeogenesis at the expense of both injected and endogenous amino acids; a progressive ketosis without any associated improvement in protein economy; fat oxidization to meet caloric need.

The changes in plasma amino acid concentrations are of outstanding interest. They demonstrate changes appropriate to the infusion gradient with the exception of three amino acids whose concentrations did not respond to high infusate levels (serine, lysine, alamine); likewise by the fact that methionine rose remarkably though present in low concentrations in the infusion. These data taken with other information reported in the literature, strongly suggest that the utilization of infused amino acids for protein synthesis is favored by the provision of an additional caloric source such as glucose.

Substrate Interactions

The studies of the comparative effects of carbohydrate and fat on amino acid utilization in fasting man have also been concluded and published. Data are presented on the metabolic and endocrine effects of intravenous infusions in normal fasting man observed under highly controlled conditions over a period of six to eight days duration. There are comparative data on a variety of intravenous feeding programs. The data on total starvation are based on studies from the literature, some of which were carried out in this laboratory. The data on low dose glucose, high dose glucose, glycerol, fat emulsion, and amino acids, each given separately, demonstrate changes seen with simple infusion of a single substrate in fasting. These data are now compared with the utilization of amino acid infusions when accompanied by low dose glucose, high dose glucose, glycerol, and fat emulsion. In all, nine experimental intravenous feeding programs are presented, based on data from 35 subjects observed over a total of 370 subject-days. The findings show a strong interaction between glucose or lipid and protein metabolism. In fasting, glucose had protein sparing effect, most evident when given at high dose. Glycerol, in an amount equal to that contained in 2000 ml of ten percent fat emulsion, had a mild protein sparing effect. Fat emulsion was no more effective. When amino acids were given alone, normal fasting human subjects were always in negative nitrogen balance with the daily nitrogen loss half that seen in starvation alone. Although amino acids given alone have a protein sparing effect, this is accomplished only at the expense of a high nitrogen excretion including an amount equivalent to the entire infusion plus an additional loss from the body's native proteins.

The provision of energy yielding non-protein substrates with the amino acids markedly improved nitrogen economy in the following order: glycerol, low dose glucose, fat emulsion and high dose glucose. When caloric provision with glucose approached the isocaloric level for normal diet, the utilization of amino acids was maximized. When given with amino acids, fat emulsion was more effective than the available glycerol alone.

The accompanying endocrine and biochemical changes suggest that the milieu for ideal utilization of infused amino acids is

variable: ketones at low range (carbohydrate) or moderately elevated (fat emulsion); insulin elevated (carbohydrate)or unchanged (fat emulsion). The utilization of the infused amino acids was markedly improved in both endocrine settings, suggesting that it is the provision of energy as substrate as well as the endocrine setting that determines amino acid utilization. There were other changes in plasma intermediates, particularly fatty acids, glucose and urea, all consistent with the concept that when amino acids are given without other substrates, the amino acids must be maximally utilized for gluconeogenesis. When other substrates are provided (particularly glucose at high dose) then this mandate no long exists and protein synthesis from the amino acids is favored.

Several of the plasma amino acid concentrations responded to glucose when added to amino acid infusion. Amino acids alone produced increases in concentration of all the amino acids found in the infusion with the exception of alanine, arginine, and threonine. Many of these increases were abated by the addition of glucose to the amino acid infusion, suggesting an increased utilization rate. Glycerol and fat emulsion, while modulating increases in the plasma amino acid concentration, did so to a lesser extent than did glucose. This lowering of amino acid concentration was unaccompanied by an increase in urinary excretion. The assumption is therefore made that the provision of the added glucose favors the incorporation of amino acid into protein. There is no evidence from these data to suggest that a rising concentration of ketones in the blood favors amino acid utilization or protein synthesis.

## II PULMONARY STUDIES

### Lung Water Changes After Thermal Burns

This study of sequential measurements of lung thermal volume was used to examine the natural history of pulmonary water changes with burn injury and its treatment. The study comprises results from nine patients with major thermal burns (20-80% body surface area). As soon as possible after initiation of acute-phase therapy LTV measurement was begun and repeated at least twice daily. Instead of the ordinary single lumen peripheral arterial catheter, a double lumen 5 French catheter placed in the radial artery by direct cutdown was used. The catheter was advanced until a phasic conductivity flow signal was obtained. The second lumen carried leads to a thermistor bead and platinum ring conductivity electrodes at the tip of the catheter. The lung thermal volume (LTV) was measured by the double indicator-dilution technique. The intravascular indicator was hypertonic saline solution which causes a change in blood conductivity measured by the conductivity electrodes. The extravascular indicator was a temperature pulse of cold water measured by the termistor bead.

Most of the measurements of LTV in these patients yielded values that lay between normal and a range of clinical pulmonary edema. Frequently the lung thermal volume reached a maximum value within the first 24 hours and by 36 hours had declined to a minimum value at the same time the peripheral burn edema was at a maximum. Pulmonary capillary wedge pressures during acute phase therapy never exceeded 10 mm Hg in any patient. Therefore the increase in LTV represented a low pressure pulmonary edema. The initial high value of LTV is presumed to be the result of alveolo-capillary damage from inhaled or burn generated toxins. There was a secondary increase in LTV associated with dilutional hypoproteinemia during edema mobilization.

The possibility that pulmonary damage is caused by burn toxin is speculative but would help explain the very early increases in LTV that were observed. With or without a toxic component it appears that a moderate increase in pulmonary extravascular water is common in burn patients and universal in the group of patients studied here. It appears early in the course of injury, and is not high pressure pulmonary edema but is associated with dilutional hypoproteinemia. It appears early and subsides early to a minimum value at the time peripheral burn edema is maximum. Secondary increase may be associated with burn edema mobilization.

Pulmonary Function Studies Following Thermal Injury

Carbon monoxide poisoning and metabolic acidosis often constitute the major problems in early treatment of fire victims with smoke inhalation. Recently, there has been interest in defining prognostic factors in patients with carbon monoxide poisoning. Studies from other laboratories have suggested that carbon monoxide poisoning associated with an arterial blood pH below 7.4 led to early mortality or to serious neurologic sequellae if the patient survived. In this study of the pulmonary function changes seen with burns and smoke inhalation, three patients with severe acidemia and high carboxyhemoglobin levels were singled out for detailed review. All three patients were admitted with carbon monoxide saturation levels greater than 40%, and pH values below a level of 7.3. The patients were managed conservatively with prompt endotracheal intubation, ventilation and the administration of a hundred percent oxygen. All three patients survived without neurologic deficit.

Obstructive lung disease was the major problem in the convalescent care of the three patients. Pulmonary function tests performed during their initial hospitalization and up to six months after the time of injury revealed a severe obstructive ventilatory defect in these patients. This defect was minimally responsive to the administration of bronchodilators. This severe obstructive ventilatory defect is highlighted by marked decreases in forced vital capacity, forced expired volume, and reduction in maximal mid-expiratory flow rate. These findings contrast with those of other laboratories which have shown normalization of pulmonary function despite severe inhalation injury.

Patients with the combination of high levels of carboxyhemoglobin and low blood pH are effectively treated with intubation and ventilation with 100% oxygen. This therapy effectively prevents neurologic deficits, but does not obviate long term respiratory problems.

BIBLIOGRAPHY

1. Morgan,A.P., Knight,D., O'Connor, N.E.: Lung water changes after thermal burns: An observational study. Ann. Surg., 187: 288, 1978.

2. Sim,A.J.W., Wolfe,B.M., Young,V.R., Moore,F.D.: Studies with $N^{15}$ glycine: Effects of glucose on the utilization of intravenous amino acids. (In preparation)

3. Strohl,K., Feldman,N., Saunders,N., O'Connor,N.E.: Carbon monoxide poisoning: A reappraisal of prognosis. J. of Trauma, (In press)

4. Tweedle,D.E.F., Fitzpatrick,G.F., Brennan,M.F., Culebras,J.M., Wolfe,B.M., Ball,M.R., Moore,F.D.: Intravenous amino acids as the sole nutritional substrate. Ann. Surg., 186: 60, 1977.

5. Wolfe,B.M., Culebras,J.M., Sim,A.J.W., Ball,M.R., Moore,F.D.: Substrate interaction in intravenous feeding: Comparative effects of carbohydrate and fat on amino acid utilization in fasting man. Ann. Surg., 186: 518, 1977.

6. Wright,P., Moore,F.D.: The effect of glucagon, norepinephrine, hydrocortisone and insulin on glucose dynamics in man using (2-$^{3}$H) glucose as the tracer. (In preparation)

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

# REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

| | |
|---|---|
| 1. REPORT NUMBER: 1 | 2. GOVT ACCESSION NO. |
| 3. RECIPIENT'S CATALOG NUMBER | |
| 4. TITLE (and Subtitle): A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA | 5. TYPE OF REPORT & PERIOD COVERED: Annual Summary Report 2/1/77 - 1/31/78 |
| | 6. PERFORMING ORG. REPORT NUMBER |
| 7. AUTHOR(s): Francis D. Moore, M.D. and Nicholas E. O'Connor, M.D. | 8. CONTRACT OR GRANT NUMBER(s): DADA-17-73-C-3022 |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS: Department of Surgery of Harvard Medical School at the Peter Bent Brigham Hospital 721 Huntington Avenue, Boston, Mass. 02115 | 10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 11 17 Feb 79 |
| 11. CONTROLLING OFFICE NAME AND ADDRESS: U.S. Army Medical Research and Development Command Washington, D. C. 20314 | 12. REPORT DATE: February 17,1979 |
| | 13. NUMBER OF PAGES: 8 (12) 11p |
| 14. MONITORING AGENCY NAME & ADDRESS (If different from Controlling Office): (9) Annual summary rept. no. 1, 1 Feb 77-31 Jan 78, | 15. SECURITY CLASS. (of this report): Unclassified |
| | 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE |

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release, distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

| | | |
|---|---|---|
| amino acids | glucose | ketosis |
| carbon monoxide poisoning | glycine | lung thermal volume |
| catabolic hormones | fat emulsion | protein sparing |
| | hyperglycemia | pulmonary water changes |
| gluconeogenesis | hypoglycemia | total body protein turnover |

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Studies were performed which showed that amino acid infusions alone did not eliminate negative nitrogen balance and that addition of glycerol, low dose glucose, fat emulsion and high dose glucose were effective in further reducing nitrogen loss with high dose glucose and amino acids being the most effective. Using $N^{15}$ enriched glycine the addition of glucose was shown to increase the rate of protein synthesis over amino acid infusions alone.

(continued)

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

20. ABSTRACT

Studies with labelled glucose showed that the hyperglycemia seen with glucagon, norepinephrine and hydrocortisone infusion was due to increases in minimum glucose mass and glucose turnover. Whereas the hypoglycemia of insulin infusions resulted partially from increase in glucose space.

Studies of acute thermal burns showed an increase in pulmonary water which appeared in the first 12 hours, subsided to a minimum by 36 hours and had a secondary peak with readsorption of peripheral edema. Studies of patients with carbon monoxide poisoning showed that patients can develop a long standing obstructive ventilatory defect.