INTRAVENOUS HYPERALIMENTATION

george cowan jr.
and
walter scheetz

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Edited by

GEORGE S. M. COWAN, JR., B.A., M.B., Ch.B.

Major, MC
Chief, Shock and Trauma
Research Branch
Surgical Research Division
Surgical Directorate
United States Army Medical Research and Development Command
Washington, D.C.

and

WALTER L. SCHEETZ, M.D.

Lt. Col., MC
Chief, Surgical Research Division
Surgical Directorate
United States Army Medical Research and Development Command
Washington, D.C.

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Some hae meat and canna eat,
And some wad eat that want it;
But we hae meat, and we can eat,
And sae the Lord be thankit.

The Selkirk Grace
ROBERT BURNS

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Foreword

Intravenous hyperalimentation, the first technique of total parenteral nutrition to allow achievement of normal growth and development in infants and immature animals, as well as positive nitrogen balance, weight gain, and accelerated wound healing in adults, has rekindled the interest of basic scientists and clinicians in parenteral nutritional and metabolic management of patients with trauma or disease.

The primary purposes of the Intravenous Hyperalimentation Conference were as follows: (1) to define and determine the role of intravenous hyperalimentation in the care of combat casualties and civilian patients, (2) to provide a comprehensive and definitive review of the present "state of the art" of intravenous hyperalimentation, and (3) to discuss the most promising future avenues of clinical and laboratory investigation into the art and science of intravenous nutrition. The many and varied reports and discussions of the participants in this Conference cover a wide range including the history, theory, indications, technical considerations, complications, risks, and current and future applications of the technique. All are collected in this volume.

Intravenous therapy had its inception more than three centuries ago when William Harvey first described the circulation of the blood in 1616. After this discovery it was logical to assume that the vascular system was the transport network by which water, nutrients, oxygen, and all the other requirements of cells were delivered to them, and the waste products of metabolism were carried away and excreted. Forty years later, Sir Christopher Wren used a goose quill attached to a pig's bladder as an intravenous administration set to introduce substances such as ale, opium, and wine into the veins of dogs. In 1662, Richard Lower reported his experiments with intravenous infusions and blood transfusion in animals,

and five years later Jean-Baptiste Denis performed the first documented transfusion of blood from a lamb to a human being. When one realizes that, at that time, there was no understanding of microorganisms, sterilization, asepsis and antisepsis, no knowledge of blood types or crossmatching, no knowledge of pyrogens and very little of the chemistry or of the osmotic effect of various solutes on erythrocytes, the audacity of these early experiments is astounding. It is not surprising that legal and clerical restraints were imposed upon attempts at blood transfusion in man following the vast number of complications and deaths which occurred because of the ignorance of the basic fundamentals known today.

The accumulation of the important bits and pieces of knowledge essential to the design of parenterally administered nutrient solutions was the result of the ingenuity and considerable effort of many investigators. In 1831 Thomas Latta infused saline solution to treat the intractable diarrhea of his patients with cholera, becoming the first man to use intravenous infusion as a successful mode of parenteral therapy. In 1843 Claude Bernard infused sugar solutions into animals for the first time, and over the span of the next 20 years was the first to inject egg albumen, milk and other nutrients into animals with a moderate degree of success. During the Canadian cholera epidemic in 1873, Edward Hodder injected milk intravenously into man with good results. In 1891, Rudolph Matas reported the first intravenous infusion of saline solution for the treatment of surgical shock in man. Five years later, dextrose was injected into the veins of human beings for the first time by Biedl and Kraus. Although the techniques and methods of parenteral therapy increased in popularity throughout the world, intravenous infusions could not be undertaken with uniform safety until the discovery of basic concepts of microbiology by Louis Pasteur and the subsequent application of the principles of asepsis and antisepsis by Sir Joseph Lister.

The intravenous infusion of dextrose for nutritional purposes following surgical procedures in man was first accomplished by Kausch in 1911. However, the problems with the infection and pyrogens were not adequately understood, and there was no uniformity of successful nutrition through use of the intravenous route. In 1914, the demonstration by Henriques and Anderson of the utilization of intravenously injected hydrolyzed protein in animals was a step forward in intravenous nutrition as it is known today. Fat was infused as a nutrient in animals by Murlin and Riche in 1915, and the clinical use of this energy substrate was made more clinically feasible by Yamakawa's work with emulsified fat infusions in man in 1920.

In 1923, the discovery of pyrogens by Florence Seibert and the clinical applications of this finding by Lee Rademaker greatly enhanced the practical intravenous administration of solutions. This launched the era of the rapid development of safe, efficacious and rational intravenous therapy which has continued for the past 40 years.

Although the excessive losses of protein nitrogen which resulted from

diseases such as typhoid fever had been documented early in the twentieth century by Coleman, in the 1930's Cuthbertson first defined the metabolic significance of the well-recognized clinical observation that, following severe trauma, there is an extraordinary loss of body weight, muscle mass and strength despite a seemingly adequate oral intake of both calories and protein. His observation that a high-protein, high-calorie diet could reduce, but not eliminate, the negative nitrogen balance which followed injury, was confirmed and extended several years later by Howard. During World War II, Robert Elman and his associates studied the effectiveness of parenteral infusion of casein hydrolysates in altering the postoperative loss of nitrogen in surgical patients. His findings, and those of Brunschweig, both showed an increased total nitrogen excretion and also a reduction in the amount of endogenous nitrogen when such preparations were used together with high-energy substrates. However, neither group of investigators was able to achieve a nitrogen equilibrium or positive nitrogen balance in any patient following major surgery if preoperative nutrition had been normal and the patients were not debilitated. Rhoads and his associates showed that nitrogen equilibrium could be achieved in many patients postoperatively when elevated levels of protein and calories were administered. Similar results were achieved by Mulholland and his associates, and a few years later Werner reported marked reduction of nitrogen losses and the achievement of nitrogen equilibrium in some patients following fractures or some surgical operations when large amounts of amino acids were administered by vein. However, nitrogen equilibrium or positive nitrogen balance could not be achieved uniformly because of the limited amount of calories which could be administered together with the required nitrogen moieties.

Adequate intravenous nutrition is limited by several factors. First, the volume of water which an adult patient can ordinarily utilize safely is limited to approximately 35 to 50 milliliters daily per kilogram of body weight, amounting to approximately 3 to 3½ liters per day for the average patient. Another limitation is the inherent caloric density of the nutrient; 4 calories per gram of carbohydrate or protein, 7 calories per gram of ethyl alcohol, and 9 calories per gram of fat. The third limitation is that the concentration of solute which can be infused into a peripheral vein without causing phlebitis or thrombosis is limited to 5% or 10% dextrose solutions, a range of approximately twice the isotonic concentration. In the late 1940's and early 1950's, many teams of investigators throughout the country undertook a comprehensive study of the safety and efficacy of parenteral fat as a means of providing adequate calories by vein. For the first time, intravenous feeding regimens containing vitamins, minerals, carbohydrates, amino acids or protein hydrolysates, and fat emulsions were used to provide "complete parenteral diets" in order to achieve limited positive nitrogen balance during several short-term periods of total intravenous feeding. The work of Holden, Abbott, Johnston and others all

supported the significance and effectiveness of providing 35 to 50 calories per kilogram and 0.1 to 0.2 grams of nitrogen per kilogram per day in critically ill patients. However, the initial enthusiasm for fat emulsions gave way to numerous reports that prolonged use of intravenous fat sometimes produced fever, jaundice, coagulation defects and other complications which, in 1964, eventually led to the withdrawal of the cottonseed oil emulsion from clinical use in the United States. On the other hand, soybean oil emulsions continue to be used extensively throughout the rest of the world, and the newer preparations appear to be safer and more efficacious for long-term infusion. Currently, the use of intravenous fat emulsions in the United States is restricted by the US Food & Drug Administration.

Limited positive nitrogen balance was achieved in adult patients in the early 1960's when Rhoads, Dudrick and co-workers took advantage of intravenously administered diuretics, such as chlorothiazide, to promote excretion of excess vehicular water when 5 to 7 liters of 10% or 15% nutrient solutes were administered by peripheral vein. However, because of the wide variations in water and electrolyte flux which occurred with this technique, it was eventually abandoned.

The only apparent alternative to providing adequate nutrition parenterally was to further concentrate the readily available intravenous nutrients in order to meet the high caloric and nitrogen requirements of critically ill patients, and to develop a safe and effective technique for prolonged infusion of hypertonic solutions. Because early approaches using the inferior vena cava for central venous delivery of nutrients in dying patients revealed significant clot formation around the catheter at autopsy, the technique of inferior vena caval infusion was abandoned in favor of superior vena caval infusion. In order to test the validity of the hypothesis that positive nitrogen balance could be achieved practically and effectively by providing all nutrients by central vein, Dudrick, Vars, and Rhoads designed apparatus and an experiment to determine if weanling puppies could grow, develop and thrive while being fed entirely by vein for a minimum of ten weeks. In 1965, in the laboratories of the Harrison Department of Surgical Research of the University of Pennsylvania, it was demonstrated for the first time in any animal species that normal growth and development could be achieved for prolonged periods of time by the continuous infusion of a completely intravenously administered diet into beagle puppies. Of the first six matched pairs of animals studied, the initial set was maintained for the original ten-week goal, three sets were maintained for 100 days, one set for 235 days, and another set for 256 days, stilling forever the earlier belief that it was impossible to provide adequate nutrients by vein alone and support prolonged normal growth. Attention was then directed to adapting the technique for use in man. Parenteral diets were formulated according to the nutrient requirements for growth in human infants. Through polyvinyl or silicone rubber catheters inserted into the superior vena cava, hypertonic solutions consisting of approximately 20% to 25%

dextrose, 4% to 5% fibrin hydrolysate, and 5% additional solute containing all required vitamins, minerals, and trace elements were infused intravenously by pump. Following a massive small bowel resection and transverse colon resection for congenital intestinal atresia, the first newborn infant nourished by this technique gained 3½ pounds, increased her body length 6½ cm, her head circumference 5½ cm and her chest circumference 8 cm while being supported entirely by intravenous hyperalimentation for 44 days. This case represented the first achievement of normal growth and development in man associated with long-term total intravenous feeding. Since then hundreds of infants with various congenital malformations and other conditions precluding nourishment by way of the gastrointestinal tract have been beneficially fed for prolonged periods of time entirely by the intravenous route.

Beginning with the very first adult patient supported wholly by intravenous hyperalimentation for one month, positive nitrogen balance, wound healing, weight gain and increased strength and activity have been achieved in the vast majority of more than 1,000 patients seen at the University of Pennsylvania Medical Center. In the course of providing adequate nutrition exclusively by vein for prolonged periods of time, the bowel can be by-passed, allowing secretory and mechanical rest potential advantages in a wide variety of pathological states. Heretofore, all methods utilized to rest significant portions of the gut have been accompanied by malnutrition or starvation. In our personal experience, more than 90 enterocutaneous fistulas of the alimentary tract have closed spontaneously in over 75 patients without surgery. The morbidity and mortality associated with the complications of a ruptured enteric anastomosis have been significantly decreased by this nonoperative technique of bowel rest and total intravenous feeding. In patients with pancreatic or high gastrointestinal fistulas, as much as an 80% reduction in the volume of caustic secretions has occurred within a few days after starting intravenous hyperalimentation. During the course of intravenous hyperalimentation and bowel rest preparatory to surgery in more than 40 of our patients with granulomatous disease of the small or large bowel, three-quarters of them have achieved a state of remission of their disease to the extent that the operation was cancelled. In patients with malignant disease, application of the technique of intravenous hyperalimentation has reduced anorexia, nausea, vomiting and pain, while achieving positive nitrogen balance and weight gain in many patients. It has also allowed the delivery of more than twice the usual dose of 5-fluorouracil to patients with bowel tumors because of the reduced gastrointestinal toxicity response. Patients with renal or hepatic disease have benefited from treatment with special forms of intravenous hyperalimentation. By combining intravenous hyperalimentation with various forms of alimentary tract feeding, as much as 10,000 kilocalories per day together with large amounts of other required nutrients have been administered to patients with major burns, multiple trauma and long bone fractures in

whom provision of adequate nutrients to counter the marked catabolic response was deemed critical for survival.

It seems justifiable that if patients merit any form of therapy for their pathological processes, they deserve adequate nutritional support during such therapy. The aim of such support, however, should be to promote meaningful life, and not merely to prolong inevitable death. As greater numbers of patients are supported and studied with this technique, and as its safety is maximized, it is anticipated that good studies of convalescence will evolve to define objectively the subjective impressions that morbidity and mortality can be significantly improved in standard uncomplicated surgical operations when intravenous hyperalimentation support is employed.

For many years, achievement of adequate nutrition by total intravenous feeding over long periods of time was the goal of many investigators. The ingenuity and efforts of many workers during the past few centuries have led finally to the development of a technique of total intravenous nutrition which can promote normal growth, development, and positive nitrogen balance in infants and adults for prolonged periods of time. The current technique of intravenous hyperalimentation is one which is relatively safe and efficacious, but it must undoubtedly undergo change and modification as improved methods, materials and techniques are developed. With judicious application of the technique as an investigative and therapeutic tool, the horizons for intravenous hyperalimentation will continue to expand, extending to every medical specialty and into many areas of basic research. As relatively few of the possible uses for intravenous hyperalimentation have been thoroughly explored to date, the potential for total intravenous therapy is real and exciting and appears to be limited only by the basic ingenuity and ambition of man. From the efforts reported in this volume, it is hoped that knowledge in the field of intravenous nutrition and metabolism will flourish and grow to the extent that it will no longer be necessary or justifiable that a patient not be adequately and safely nourished by vein when use of his gastrointestinal tract is inadequate, ill-advised, or impossible.

The participants of this Conference are deeply indebted to Dr. John A. Schilling, Chairman of the Surgeon General's Committee on Metabolism of Trauma, and to Major George S. M. Cowan, Jr., MC, and Lt. Col. Walter L. Scheetz, MC, of the US Army Medical Research and Development Command for their efforts and support in originating, organizing and administering the Conference and making the proceedings of this highly significant hyperalimentation Conference available to all through this volume.

STANLEY J. DUDRICK, M.D.

Preface

In this volume, we present a critical analysis of the concepts and techniques for providing prolonged high-caloric parenteral alimentation to the severely ill, injured or debilitated patient unable to receive food by mouth. The successes achieved many years ago in maintaining a positive nitrogen balance through intravenous feeding are well known. The more recent development and popularization of this nutritional modality using highly concentrated solutions have led the editors to select the title, *Intravenous Hyperalimentation,* a term that has achieved widespread currency as well as general understanding.

The selection of optimal formulations of foodstuffs that are physiologically acceptable and effective in the maintenance of patients who can survive only on prolonged parenteral feedings was a paramount concern of the Conference that was the source of these proceedings. It has become apparent that the multiplicity of nutritional problems occurring with massive trauma and debilitating disease demands a variety of specific therapeutic responses to prevent or correct formidable catabolic effects, and each such response is unique quantitatively, qualitatively, and temporally to any given patient.

Because of its experience in the treatment of large numbers of massively traumatized patients in Vietnam, the US Army Medical Corps has great interest in the development of more effective methods of intravenous hyperalimentation. The civilian medical community shares the urgent awareness that better methods are needed to obtain and maintain nutritional balance in order to prevent the sequelae of injury-induced malnutrition such as are seen in delayed wound healing, sepsis, and, all too often, death. The advent of helicopter evacuation of battlefield casualties as the common means of transporting wounded, and the employment of this means by

civilian medical centers, the state police, and other rescue units have focused attention on this problem by bringing severely injured patients to hospitals alive where survival may then require extremely complex long-term management.

A Conference on Intravenous Hyperalimentation, sponsored by the US Army Medical Research and Development Command, was held on 30 November 1970 at the US Army Institute of Surgical Research, Brooke Army Medical Center, San Antonio, Texas. Its purpose was to attempt to answer definitively some of the questions in this area and provide a review of current concepts in intravenous hyperalimentation, while at the same time stimulating further research in the nutritional problems of surgical patients. This work is an example of the continuing close liaison and cooperation of the US Army Medical Corps with the civilian medical research community in their common endeavor to define and solve the infinite problems of surgical and medical treatment.

We wish to thank all of the participants and contributors who gave so generously of their time and expertise to the Conference and publication of these proceedings. Chief among these were the members of The Advisory Committee on Trauma to The Surgeon General of the Army. Dr. John A Schilling, Committee Chairman, deserves special praise and thanks for his help and enthusiastic support.

The invaluable advice, sound judgment and patience of our immediate superior, Colonel Daniel W. Pratt, MC, Director of Surgical Research, Surgical Directorate of the US Army Medical Research and Development Command (USAMRDC) were outstanding and elemental in bringing the Hyperalimentation Conference and this book to fruition. Our Commanding General, Brigadier General Richard R. Taylor, MC, and his Deputy, Colonel Kenneth R. Dirks, MC, were also extremely helpful.

The hospitality of Brigadier General Kenneth D. Orr, MC, Commanding General of the Brooke Army Medical Center, was gracious and complete in every respect. Lieutenant Colonel Basil A. Pruitt, Jr., MC, Commanding Officer of the US Army Institute of Surgical Research, his Executive Officer, Major Harold W. Powell, MSC, and their staff looked after every detail, coordinated thoughtfully at every turn, and anticipated all problems in an outstanding fashion. The entire program committee is to be warmly congratulated for their most significant help. Drs. John Kinney, Louis Plzak and Stanley Dudrick, program committee members not mentioned above, rendered particularly valuable assistance for which we are most grateful. We are indebted to Dr. Dudrick for additionally consenting to write the Foreword and Introduction. Discussion Chairmen, Drs. John Schilling, George Cahill, Jr., John Border, Basil Pruitt, Richard Mason and John Kinney produced an outstanding interchange between the participants of the Conference, especially in view of the extreme time limitations.

Martin W. Barnes, Chief, Medical Audio-Visual Branch, US Army Institute of Surgical Research, handled the tape-recording of the entire Con-

ference and kindly furnished us with copies of good quality to assist in the preparation of this book; our sincere thanks are extended to Mr. Barnes and his assistants.

Not to be forgotten in our thanks are our publishers, Lea & Febiger, whose editors, Edward Wickland, Martin Dallago and Thomas Colaiezzi, were a mainstay in our efforts.

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Washington, D.C.

GEORGE S. M. COWAN, JR., M.D.
WALTER L. SCHEETZ, M.D.

Contributors

Terry R. Allen, M.D.
Assistant Instructor in Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

T. T. Aoki, M.D.
Instructor in Medicine
Peter Bent Brigham Hospital
Harvard University
Boston, Massachusetts

John R. Border, M.D.
Professor of Surgery
State University of New York
Buffalo, New York

B. H. Bowser, B.S.
Department of Surgery
University of Arkansas Medical School
Little Rock, Arkansas

George F. Cahill, Jr., M.D.
Professor of Medicine
Deaconess Hospital, Joslin Clinic
Boston, Massachusetts

Frederick T. Caldwell, M.D.
Professor and Chairman
Department of Surgery
University of Arkansas Medical School
Little Rock, Arkansas

Lars Carlson, M.D.
Professor
Uppsala University
Uppsala, Sweden

R. Casali, M.D.
Research Fellow, Department of Surgery
University of Arkansas Medical School
Little Rock, Arkansas

Countee Collins, SSG
US Army
Washington, D.C.

P. William Curreri, Major, MC
US Army Institute of Surgical Research
San Antonio, Texas

John M. Daly, A.B.
Research Associate in Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

William R. Drucker, M.D.
Professor and Chairman
Department of Surgery
The Banting Institute
University of Toronto
Toronto, Canada

Stanley J. Dudrick, M.D.
Associate Professor of Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

John M. Kinney, M.D.
Professor of Surgery
College of Physicians & Surgeons
Columbia University
New York, New York

James M. Long, M.D.
Assistant Instructor in Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Bruce McGovern, M.D.
(Formerly Major, MC, USAF, Lackland AF Base)
Surgeon
San Antonio, Texas

Joseph Judson McNamara, Major, MC
Professor of Surgery
University of Hawaii School of Medicine
Honolulu, Hawaii

Mark D. Molot, Major, MC
Department of Experimental Pathology
Walter Reed Army Institute of Research
Washington, D.C.

Francis D. Moore, M.D.
Moseley Professor and Chairman
Department of Surgery
Peter Bent Brigham Hospital
Boston, Massachusetts

Hamish N. Munro, M.D.
Professor
Massachusetts Institute of Technology
Boston, Massachusetts

Louis F. Plzak, M.D.
Professor of Pediatric Surgery
Jefferson Medical College
Philadelphia, Pennsylvania

William J. Rea, M.D.
Professor of Surgery
University of Texas Medical School
Dallas, Texas

Jonathan E. Rhoads, M.D.
John Rhea Barton Professor and Chairman of the Department of Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Robert L. Ruberg, M.D.
Assistant Instructor in Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

John M. Schilling, M.D.
Professor and Chairman
Department of Surgery
University of Oklahoma Medical Center
Oklahoma City, Oklahoma
Chairman, The Surgeon General's Committee on Trauma

George Sheldon, M.D.
Assistant Professor of Surgery
University of California, San Francisco
San Francisco, California

Ezra Steiger, M.D.
Assistant Instructor in Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

John F. Stremple, Major, MC
Assistant Professor of Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Harry M. Vars, Ph.D.
Professor of Biochemistry in Surgical Research
Harrison Department of Surgical Research
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

George Watkins, M.D.
NIH Post-doctoral Fellow in Surgery
Department of Surgery
Peter Bent Brigham Hospital
Boston, Massachusetts

Douglas W. Wilmore, M.D.
Harrison Department of Surgical Research
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

David Wissman, SP5
US Army
Washington, D.C.

Panel Chairmen

John M. Schilling, M.D.
Professor and Chairman
University of Oklahoma
Department of Surgery
Oklahoma City, Oklahoma
Chairman, The Surgeon General's Committee on Trauma

George F. Cahill, Jr., M.D.
Professor of Medicine
Harvard University
Boston, Massachusetts

John R. Border, M.D.
Professor of Surgery
State University of New York
Buffalo, New York

Basil Pruitt, Jr., Lt. Col., MC
Commanding Officer
Institute of Surgical Research
San Antonio, Texas

Richard Mason, Ph.D.
Chief, Division of Surgical Laboratories
US Army Institute of Surgical Research
San Antonio, Texas

John M. Kinney, M.D.
Professor of Surgery
College of Physicians & Surgeons
Columbia University
New York, New York

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