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REFRACTORY HYPOTENSION

J. KEITH WELBORN, M.D.* AND JOSEPH L. PONKA, M.D.**

PHYSICIANS MANAGE the hypotensive state with great facility in the majority of cases. A large group of patients are seen with obvious lesions which promptly respond to classically prescribed methods of treatment. A smaller group of patients are seen, however, with hypotension refractory to the commonly employed resuscitative measures. These patients represent complex problems in evaluation and management. The mortality in this group has been reported to be in the range of 80 per cent.^{4,15}

The term "irreversible shock" (a description of an experimental model borrowed from the animal laboratory) popularly has been applied to human patients as an autonomous diagnosis. The term implies a state of progressive hypotension and "toxemia", the treatment for which thus far has been unsuccessful. Acceptance of the term has led to a diversion of attention from the fundamental pathogenic sequences which initiate and perpetuate hypotension. Although subtle, difficult to recognize, and associated with a high mortality, the physiologic alterations responsible for this state, more appropriately called refractory hypotension, can be treated successfully.

Management of refractory hypotension is one of the most challenging problems the physician sees. We have attempted to review its pathophysiology by reducing complex physiochemical processes to simplest terms so that a logical approach to the problem in a given patient might be made.

HISTORY

Hippocrates recognized the prognosis of patients with multiple traumatic injuries who displayed visible evidence of shock. Ambroise Pare wrote of "Syncope and Heart Failure" in describing the picture of neurogenic shock. James Latta of Edinburgh, 1795, is given credit for the first use of the word shock.

Shock was described as a clinical state in the 16th, 17th and 18th centuries. Glowes 1568, Wiseman 1719, and Garengiot 1723 attributed shock to the presence of some foreign matter in the wound or blood. The Civil War surgeons, Weir Mitchell, Morehouse, and Keen referred to shock as a "reflex disturbance". Billroth described

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a "molecular disturbance of the brain." Blum referred to reflex cardiac inhibition due to vagal irritation. Benjamin Travers is credited by Blalock² to have made a major contribution to the understanding of shock in his time. His book, "An Inquiry Concerning That Disturbed State of Vital Functions Usually Denominated Constitutional Irritation" published in 1820 disagreed with the accepted teachings of his eminent contemporaries (John Hunter, Broussais, and his teacher, Sir Astley Cooper) who were advocates of blood letting.

In 1899 Crile published his first book describing what was later called the Crile-Mummery Hypothesis. In it, shock was ascribed to nervous exhaustion in an electro-chemical system with two poles, the brain and liver. In shock the electrical conductivity of the brain was described as decreased and that of the liver increased. Crile's efforts attempting to block painful stimuli resulted in a significant reduction of trauma associated with surgical procedures and handling of patients in shock, although his concept of a primary etiologic mechanism was refuted.

Gray and Parsons, 1912, and Janeway and Ewing, 1914, concluded with experimental data that nerve cell exhaustion played no role in the pathogenesis of shock.

Malcolm, in reports published as early as 1893, demonstrated the constriction of peripheral vessels in shock and made two important observations based on clinical rather than experimental work: 1) The danger to vital structures imposed by prolonged intense vasoconstriction. He advised against the use of vasoconstrictors therapeutically. 2) The principle of diminution of intravascular fluid volume in shock.

Mann, 1915, discussed the concept of "bleeding volume" (and thus inferentially blood volume). At this time it can be seen that a shift of emphasis from CNS depression to circulating volume loss was taking place.

Porter, 1916, described the importance of the diastolic pressure on prognosis in shock and in 1917 described fat embolism as a cause of shock (previously mentioned by Mausell-Moullin in 1894). Guthrie, 1917, discussed the significance of vasomotor tone in shock.

Henderson, 1917, described decreased tissue metabolism as measured by oxygen uptake in burn shock and described hypothermia as a result of shock.

Dale and Laidaw in 1910, studied the effect of histamine, peptones, and pressor amines in shock.

The work of Erlanger, Gesell, Gasser, Meek, Cannon, Bayliss, Phemister, and Parsons added greatly to our knowledge of blood volume changes, replacement methods and experimental technique.

REFRACTORY HYPOTENSION

The contributions of Blalock made as early as 1927 form the foundation for some of the basic pathophysiology of shock as we know it today. Blalock and Phemister, 1928, showed the importance of loss of fluid from circulating volume into extravascular tissue space due to local trauma. They suggested the possibility of two types of hemorrhage:

- 1) Outside of the body
- 2) Into the tissues

Their findings were based on a repeat of work done previously, 1919, by Cannon and Bayliss, who had erroneously concluded that increase in the weight of a traumatized dog hind limb due to local fluid accumulation was insufficient to cause shock. Blalock and Phemister, 1928, and subsequently Parsons and Phemister, 1930, demonstrated the importance of this phenomenon and showed that the original work failed to include the areolar tissue of the groin where the fluid had migrated and thus had not been included in the traumatized limb weight.

Johnson and Blalock, 1931, demonstrated the importance of a time relationship between "secondary shock" and "histamine shock". Blalock, et al., 1934, demonstrated the importance of rate of blood loss to onset of signs of shock.

Blalock's concept of shock was: "A clinical syndrome, the features of which are familiar to all, resulting in inadequate blood supply to the tissues of the body, occurring as a result of underlying disturbances of different systems." With this as a basis, he classified shock as: hematogenic, neurogenic, vasogenic, cardiogenic, and unclassified.²

Gregerson and Gibson in 1937, reported a method for estimation of blood volume using Evans Blue Dye (T-1824).

More recently, numerous important contributions have been made from the laboratory and clinical work done by Simeone, Fine, Moore, McLean, Lellehei, Altmeier and Thal.

Throughout the history of the study of shock confusion has persisted regarding initiating, accompanying and perpetuating factors.

Even more confusion evolves from a discussion of the semantics of the definition of shock. Some deplore the use of the word "shock." However, "shock" carries with it a connotation of a clinical state which is distinct to experienced clinicians. We think it matters little which word is used to denote this state, which has as its common feature decreased tissue perfusion.

Tissue Perfusion _____ depends on ...

- Blood Pressure
- Number of Patent Vessels
 - diameter
 - length
 - contractility
- Constituents & Properties of Blood

Figure 1

Pump Deficiency

- Pre - Existing Myocardial Damage
- Coronary Occlusion
- Cor Pulmonale
- Cardiac Tamponade
- Cardiac Contusion
- Diminished Coronary Flow
- Toxic Injury
 - Hypoxemia
 - Bacterial Toxins
 - Metabolic Toxicity
 - Deficiency of Metabolic Substrates

Figure 2

REFRACTORY HYPOTENSION

ETIOLOGY

The final common path in the refractory hypotensive state is persistent deficient tissue perfusion. This is perpetuated by decreased blood flow in the most terminal peripheral vessels. Perfusion of a segment of tissue depends upon: 1) Arterial pressure; 2) the number of patent vessels supplying the tissue, their diameter, length and contractility; and 3) the proper constituents and physical properties of blood. (Figure 1.)

The maintenance of tissue perfusion depends upon three factors: 1) efficiency of the *pump*; 2) adequacy of the blood *volume*; and 3) peripheral *resistance*.

THE PUMP

Pump efficiency can be diminished by pre-existing myocardial damage, acute coronary occlusion, cor pulmonale, cardiac tamponade, contusion, severely diminished coronary artery flow and toxic injury due to hypoxemia from its number of causes, bacterial toxins, metabolic toxins, and deficiency of metabolic substrates necessary for normal muscle contraction. (Figure 2.)

Figure 3 shows the four major categories of pump deficiencies: infarction, tamponade, cor pulmonale, and toxic injury. Familiar with these possibilities, the physician can be thorough and prompt in the evaluation of his patient with shock.

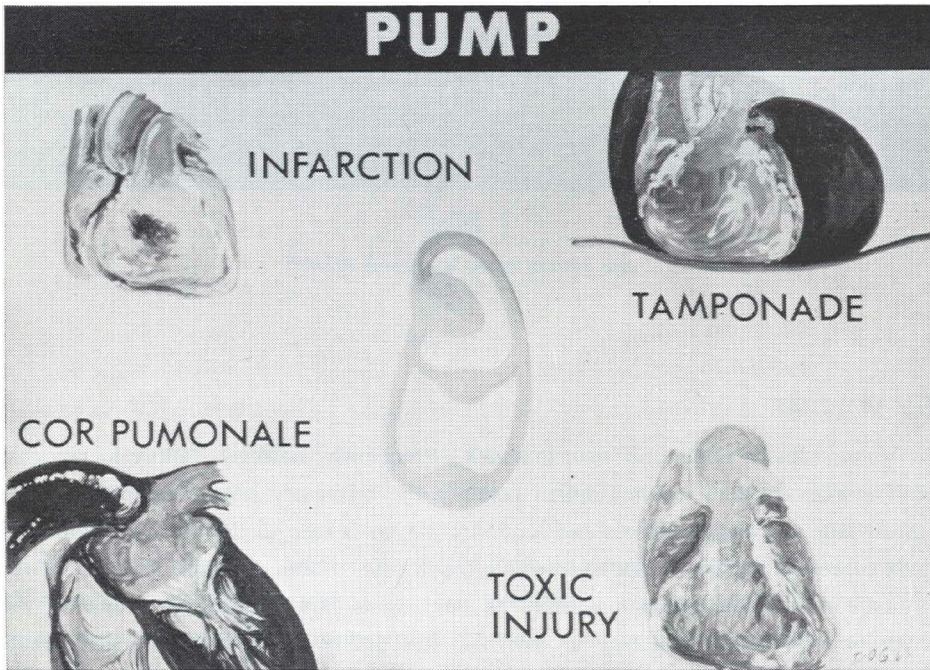


Figure 3
Four major categories of pump deficiencies.

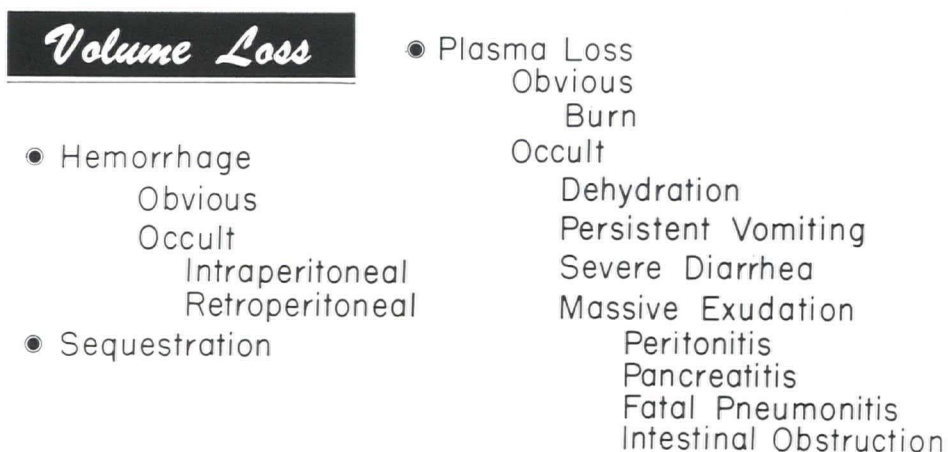


Figure 4

THE VOLUME

Volume loss is commonly seen in shock. Frequently, however, failure to recognize occult sources of blood volume deficit result in the refractory state. Hemorrhage from both obvious and occult sources and sequestration, as is seen in the burn and endotoxin shock, represent the possibilities for whole blood loss. Plasma volume loss, not always as apparent as whole blood loss, may be obvious as in the burn, or occult as with dehydration, persistent vomiting or diarrhea. Exudation losses are frequently greater than expected in peritonitis, pancreatitis, fatal pneumonitis, and intestinal obstruction. (Figure 4).

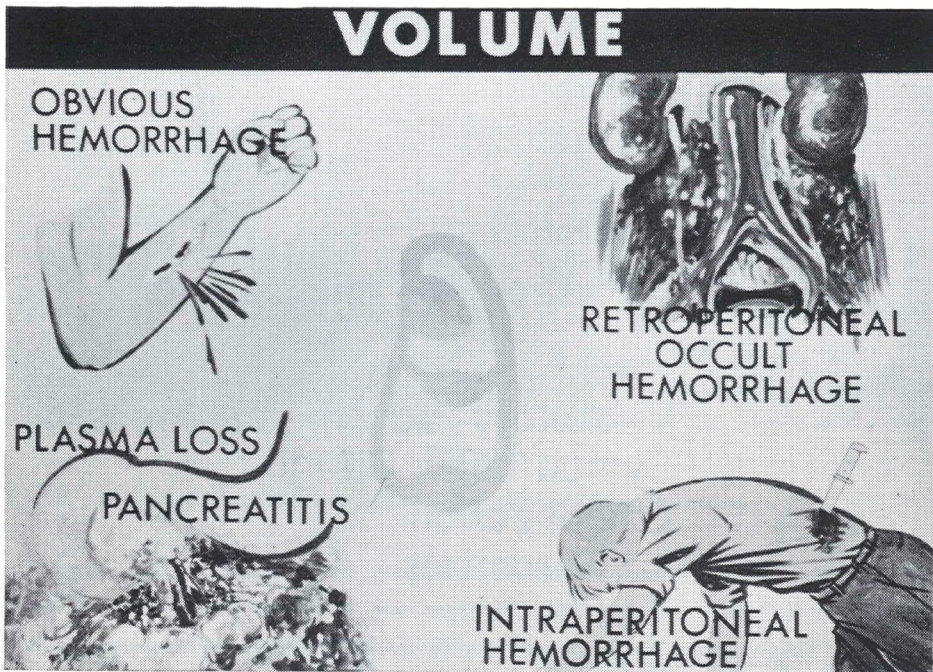


Figure 5

Possible sources of occult plasma loss.

All areas of possible volume loss should be considered in evaluating each patient with shock, since multiple sources of loss commonly co-exist. In the absence of obvious hemorrhage, occult sources must be ruled out, such as intraperitoneal, retroperitoneal, and associated with long bone fractures, the possible sources of occult plasma loss are represented by the picture of fulminant pancreatitis. (Figure 5).

Peripheral Resistance

- Direct Vascular Cytotoxins
 - Chemical
 - Metabolic
 - Immunogenic
 - Radiation
 - Bacterial
- Local or Regional Hypoxemia
- CNS Injury
 - Medullary Vasomotor Areas
 - Sympathetic Ganglia
 - Embolization
 - Thrombus
 - Fat
- Anesthesia

Figure 6

THE RESISTANCE

Deterioration of peripheral resistance occurs frequently, associated with or as a result of prolonged hypotension. Vascular cytotoxins directly affecting vasomotor stability fall under the general headings of chemical, metabolic, immunogenic, irradiation, and bacterial. Local or regional hypoxemia from toxic or ischemic injury may be important. Central nervous system injury, particularly to the medullary vasomotor areas, the sympathetic ganglia and reflex injury associated with intracerebral embolization may precipitate rapid collapse of peripheral resistance. Anesthesia is included as a separate category because of its iatrogenic nature. (Figure 6).

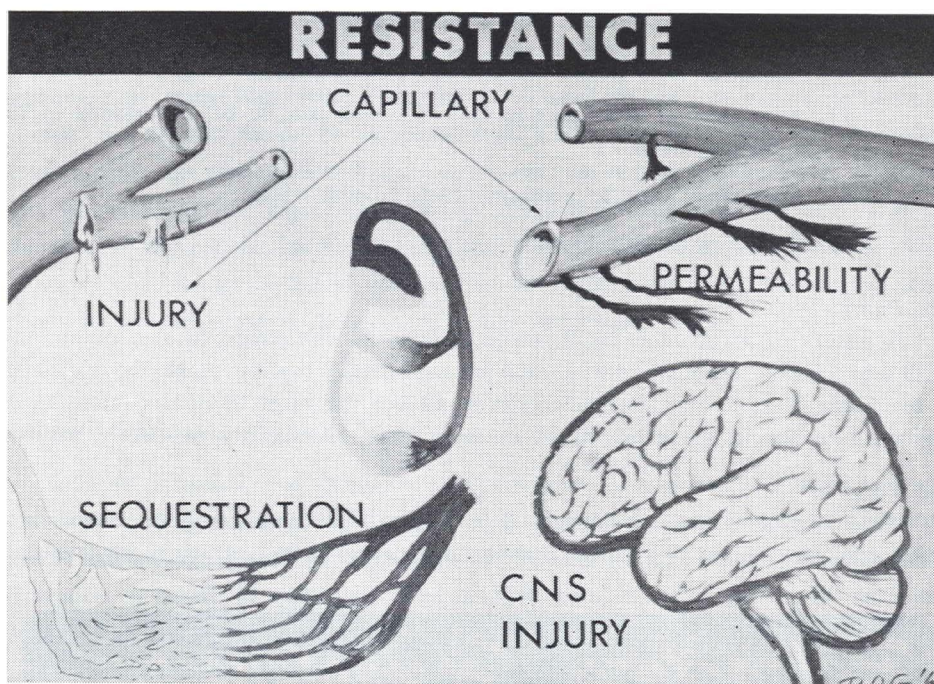


Figure 7

Three major categories of decreased peripheral resistance.

Three major categories of decreased resistance should be considered. Toxic injury affecting the precapillary and capillary cells and the more subtle causes of capillary permeability represent direct cellular insult. CNS injury which may be the result of hypoxia due to trauma, vascular accident, or anesthesia results in reflex sympathetic block. Sequestration, localized increase in vascular capacity, is encountered commonly in burns and endotoxin shock. (Figure 7).

THE REFRACTORY STATE

All of the factors known to be responsible for the refractory state should be considered in the evaluation of each patient with hypotension of occult etiology. Multiple processes may result in a complex physiometabolic interaction which can be reversed when each is attacked individually. Or, a single factor may be missed if each is not considered carefully. Advanced age, pre-existing myocardial disease, occult blood volume deficit, invasive infection, renal failure, electrolyte and acid-base imbalance are the factors most frequently associated with refractory hypotension. With the exception of advanced age, each category can, if recognized, be treated successfully. (Figure 7.)

TREATMENT

Successful management of refractory hypotension depends on:

- 1) Awareness of the multiple factors which can be of importance in the patient at hand.
- 2) Aggressive steps to eliminate each possible factor.
- 3) Precise aggressive therapy.

The Pump:

A history of myocardial insult, physical signs of diminished cardiac output, the EKG and central venous pressure monitoring should rapidly make the efficiency of the pump clear to the alert physician in all but the most unusual circumstances. Digitalization should be accomplished in most cases, particularly in elderly patients.

The Volume:

Experimental as well as clinical data suggest that occult volume deficit is a major etiologic factor in a large number of patients with refractory hypotension.

Refractory Hypotension

- Advanced Age
- Myocardial Disease
- Occult Blood Volume Deficit
- Invasive Infection
- Renal Failure
- Electrolyte Alterations
- Acid Base Imbalance

Figure 8

REFRACTORY HYPOTENSION

Sequestration of red cell and/or plasma volume (depending on the condition) may diminish the circulating volume. Therefore it is important that peripheral flow be augmented by transfusion with whole blood. Using the central venous pressure as a guide, the volume should be increased until C.V.P. reaches 20 to 25 cm. saline. In some cases this technique will "over transfuse" the patient and result in congestive signs when the patient regains integrity of peripheral vascular tone. Continued examination of the patient and C.V.P. monitoring supplemented by blood volume determinations (which can be relied upon 24 to 48 hours after stabilization) will allow proper volume adjustments to be made rather accurately.

The Resistance:

Invasive Infection:

Invasive infection may precipitate hypotension as a primary etiology, as seen commonly with gram negative septicemia. Or, bacterial endotoxins may produce severe unrelenting splanchnic vasodilatation having gained entrance to the portal circulation by means of ischemic intestinal injury resulting from prolonged mesenteric vasoconstriction due to hypotension of another primary etiology. Thus septic shock may be primary or secondary. Fine feels that septic shock is the final common path for shock of any cause, if it lasts long enough.⁴ Experimental and clinical data suggest that patients with refractory hypotension should be treated with antibiotics effective against gram negative organisms in doses regulated by the adequacy of renal function. Blood and other appropriate cultures should be obtained at the onset and continually throughout the critical period.

Renal Failure:

Prolonged hypotension, multiple rapid blood transfusions and pump oxygenator procedures can result in renal failure.¹⁸ Anticipatory treatment with Mannitol given intravenously can in most cases restore failing urinary output, if other therapeutic measures at the same time are able to maintain adequate renal plasma flow.

Electrolyte Alterations and Acid Base Imbalance:

Acute metabolic acidosis in hypotension can be due to a number of causes (Figure 9). This may be aggravated by acute or chronic respiratory acidosis. Thus the use of tracheostomy and mechanical ventilatory assistance may be imperative. Arterial pO_2 , pCO_2 and pH determinations may quickly clarify a complex problem.

Recently it has been suggested that Hydrocortisone in pharmacologic doses given intravenously is effective in refractory hypotension due to septicemia.¹⁵ We have used this regimen with success in a small number of cases.

**ACUTE METABOLIC ACIDOSIS
ETIOLOGIC FACTORS IN HYPOTENSION**

- GENERAL: Accumulation of tissue metabolites
(Lactates, pyruvates due to anaerobic glycolysis)
- BLOOD: Transfusion of old blood
Transfusion of large amounts of citrated blood
Hyponatremia due to:
 Loss of volume
 Differential loss of sodium
- HEPATIC: Injury preventing hepatic clearance of accumulating
tissue metabolic acids
- RENAL: Decreased Glomerular Filtrate
Tubular damage due to:
 prolonged hypoxemia
 precipitation of colloidal hemoglobin
 Acid Hematin
- PRE-EXISTING METABOLIC DISEASE: Diabetes Mellitus
Chronic Glomerulonephritis

Figure 9

DISCUSSION

Evaluation and management of a given patient with refractory hypotension is frequently not as easy as we would make it seem. There are some general rules which can be applied which are quite reliable.

A patient in the operative, or recently postoperative period should be considered to have occult whole blood loss. Any suggestion of respiratory functional impairment in a patient during this period, particularly if he has undergone surgery about the neck or chest wall, should be quickly investigated for tension pneumothorax and treated promptly.¹

Patients with peritonitis require in most instances vigorous whole blood, plasma, and fluid replacement. They may also manifest septic shock with little or no suggestion of the signs or sepsis.

Fractures of the long bones can be a misleading source of occult hemorrhage requiring vigorous volume replacement, particularly if other injuries co-exist.

REFRACTORY HYPOTENSION

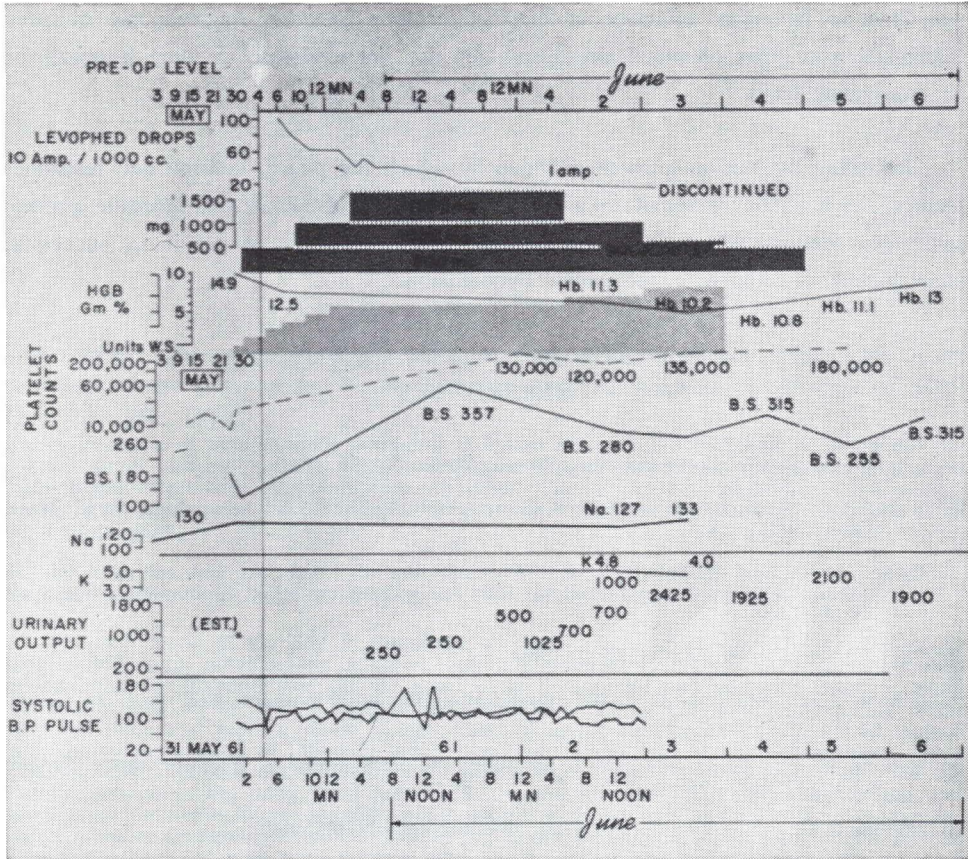


Figure 10
 Therapy in reported case of diabetes.

We have recently seen and successfully treated a patient who illustrates some of the complex problems encountered. This 71-year-old diabetic man with a history of angina developed acute profound unresponsive hypotension in the recovery room immediately following splenectomy for immunologic thrombocytopenic purpura. As can be seen from Figure 10, his treatment required the correction of occult volume loss, control of his brittle diabetes, correction of acid-base imbalance, maintenance of urine output and maintenance of adequate coronary artery perfusion.

SUMMARY

Successful management of refractory hypotension requires that the physician quickly investigate and vigorously treat his patient. The history of recent surgery, trauma, or infection should strongly suggest at least a principal etiologic factor. The physical examination of the patient should add much additional information. Appropriate laboratory data are most useful in the continued management of the patient, but are seldom helpful in the short period during which the treatment being initiated

will have to be either effective or ineffective. For instance, bacteriologic cultures, electrolyte and other chemical determinations are not available in most hospitals on an emergency basis.

Recalling the outline presented above by which the pump, volume and resistance factors can each be reviewed in a given patient, the physician can institute prompt aggressive therapy which in more instances will be likely to result in successful management of otherwise refractory hypotension.

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