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Restoration of Blood Volume Following Standard Sublethal Hemorrhage.

A. T. MILLER, JR., AND MAXINE DARK. (Introduced by John H. Ferguson.)

From the Department of Physiology, University of North Carolina Medical School, Chapel Hill.

The restoration of a normal circulating blood volume is the central problem in recovery from shock or hemorrhage. It has long been recognized that accessory factors may significantly affect the ability of the organism to restore a reduced blood volume; in many cases these factors may precipitate irreversible circulatory failure. The majority of experimental studies on shock and hemorrhage have utilized technics which produce death in untreated animals. Since the primary agent (hemorrhage, trauma, burning, or scalding) is sufficient in itself to produce death, the operation of accessory factors is difficult to evaluate. For this reason, we have adopted a standard hemorrhage of one-fourth the blood volume as the test procedure; recovery invariably occurs and restoration of blood volume follows a fairly uniform time course. The quantitative effect of accessory factors, whether favorable or unfavorable, may be estimated from alterations in the time curve of blood volume restoration.

Experimental. Normal, unanesthetized adult dogs were used. Blood volume was calculated from simultaneous values for plasma volume and hematocrit cell volume (due to uncertainty concerning the reliability of cell volume determinations in shock and hemorrhage, the results are expressed directly in terms of plasma volume). Plasma volume was determined by the dye dilution method[1] and hematocrit cell volume by centrifugation in Wintrobe tubes (1 hour at 3000 r.p.m.).

Each animal was standardized in the following manner. The normal dye disappearance curve was established from duplicate tests 1 week apart. The standard plasma volume recovery curve was constructed from the average of 2 or more experiments in which plasma volume was determined prior to, and at intervals for 4 hours following a standard hemorrhage. Post-hemorrhage plasma volume values were calculated by reference of the determined dye concentration values to the normal dye disappearance curve. Plasma volume, in percent of normal, was plotted against time in the plasma volume recovery curves. In a few experiments, animals were placed in a warm room (38-44°C) or in a cold room (4-7°C) immediately following hemorrhage to study the quantitative effect of heat and cold on the rate of plasma volume restoration.

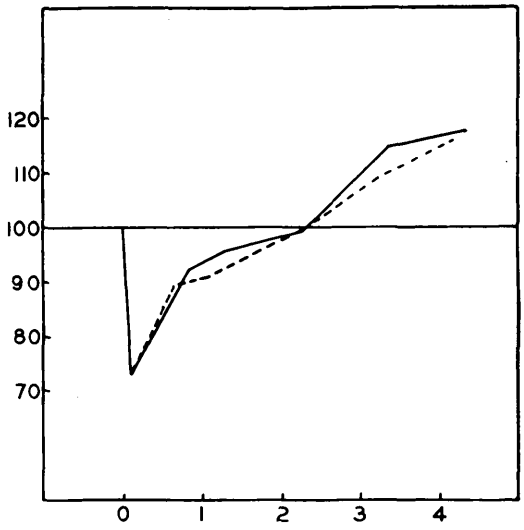

FIG. 1.

Post-hemorrhage plasma volume curves (duplicate experiments on a single animal). Ordinate: plasma volume in percent of normal. Abscissa: time in hours.

Results and Discussion. Fig. 1 shows the results of 2 experiments on the same animal and indicates the high degree of reproducibility possible under controlled conditions. In Fig. 2, the plasma volume recovery curves of 9 experiments on 5 dogs are superimposed. The variation from animal to animal, though small, is sufficient to recommend the use of each animal as its own control unless large numbers of animals are used.

[1] Gibson, J. G., II, and Evans, W. A., Jr., *J. Clin. Invest.*, 1937, **16**, 301.

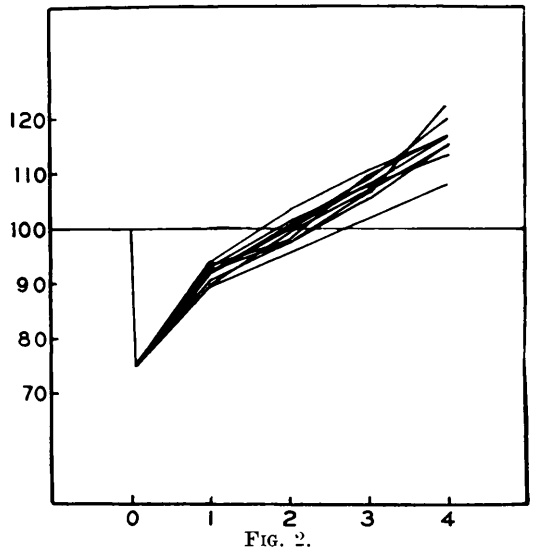

FIG. 2.

Superimposed post-hemorrhage plasma volume curves of 9 experiments on 5 animals. Ordinate: plasma volume in percent of normal. Abscissa: time in hours.

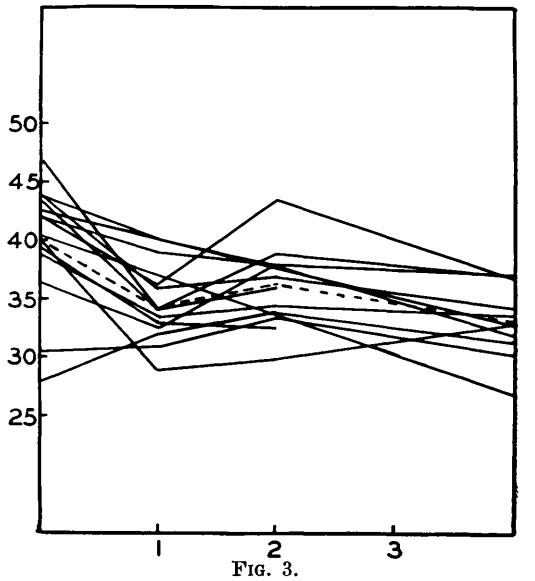

FIG. 3.

Post-hemorrhage changes in hematocrit cell volume. Ordinate: hematocrit cell volume in percent. Abscissa: time in hours.

An analysis of typical curves reveals several points of interest. (1) From 60 to 70% of the plasma lost in hemorrhage was restored during the first hour. (2) Complete restoration of plasma volume (but not of total blood volume) occurred, in the majority of experiments, in 120 to 140 minutes. This is a much more rapid recovery than that reported for the human,[2] but is in accord with the results of similar experiments on the dog[3] and rabbit.[4] (3) The recovery rate decreased during the second hour (presumably due to protein dilution) but again increased during the third and fourth hours in the majority of experiments (the explanation for this secondary increase is uncertain and is being investigated).

The hematocrit cell volume changes following hemorrhage are shown in Fig. 3. The general trend is indicative of hemodilution, but in 9 of 14 experiments hemoconcentration occurred during the second hour. The time relations make it difficult to attribute this result to release of stored cells, and emphasize the danger of relying too heavily on hemodilution as an accurate index of the rate of restoration of fluid to the blood stream.

Preliminary studies have been made on the quantitative effects of heat and cold on the rate of plasma volume restoration. Fig. 4

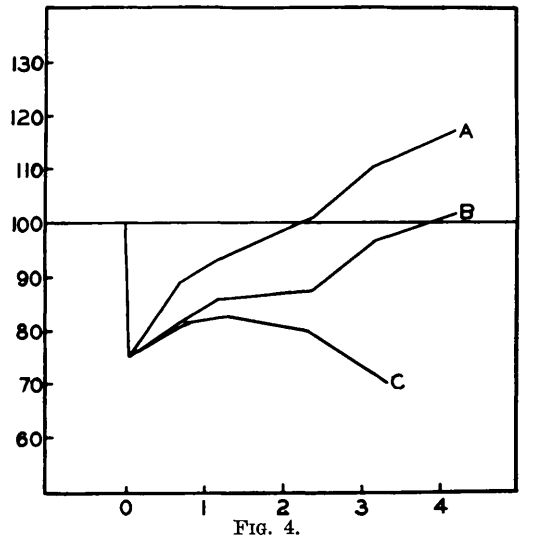

FIG. 4.

Post-hemorrhage plasma volume curves on a single animal (dog number 6). Curve A: normal. Curve B: cold room, temperature 6-7°C. Curve C: warm room, temperature 38-44°C (death occurred after 3 hours' exposure). Ordinate: plasma volume in percent of normal. Abscissa: time in hours.

[2] Ebert, R. V. Stead, E. A., Jr., and Gibson, J. G., II, *Arch. Int. Med.*, 1941, **68**, 578.

[3] Calvin, D. B., *J. Lab. and Clin. Med.*, 1941, **26**, 1144.

[4] Takahashi, S., *Tohoku J. Exp. Med.*, 1935, **25**, 531; ibid., 1935, **26**, 60.

illustrates the retarding influence of both heat and cold on recovery rate. The far more drastic effect of heat is in accord with the decreased survival time and increased mortality rate reported[5,6] under similar conditions in hemorrhagic shock. The retarding influence of cold indicates that the explanation for the increased survival time resulting from exposure to cold in hemorrhagic shock[5,6] must be sought elsewhere (it is possible that the effect of cold may depend on intensity, and that milder degrees of cooling may exert a beneficial effect).

Work in progress is designed to quantitate the influence of environmental temperature, anesthesia, anoxia, fluid balance, liver damage, and similar accessory factors on the time course of plasma volume recovery after standard hemorrhage.

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14700

Sensitivity of Various Serological (Lancefield) Groups of Streptococci to Penicillin.*

ROBERT F. WATSON (with the technical assistance of Mary Elizabeth Gardner.)
(Introduced by Homer F. Swift.)

From the United States Navy Research Unit, Hospital of The Rockefeller Institute for Medical Research.

Penicillin is now being made available in increasing quantities for the treatment of patients. This agent has been demonstrated to be of unquestionable value in the treatment of a number of human infections and to be active against an even larger number of infectious agents in experimental animals and *in vitro*. In general the effectiveness of penicillin in the treatment of infections *in vivo* is closely paralleled by its activity against the same infectious agents *in vitro*.

In previous work[1-5] dealing with the action of penicillin on streptococci *in vitro* these microörganisms have generally been classified either by their fermentation reactions or by the appearance of their colonies on blood agar. The first method is long, difficult, and often yields inconclusive results; and the second is inadequate in that each group contains a large number of antigenically unrelated strains. The Lancefield method of classifying streptococci into serological groups, based on antigenic structure, is now widely used; and groups A through N include most of the strains which have been shown to be pathogenic for man and lower animals.[6,7] In a recent report Dawson *et al.*[8] found strains of streptococci belonging

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The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

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