EFFECT OF DEHYDRATION, PRODUCED BY MERCUPURIN, ON THE PLASMA VOLUME OF NORMAL PERSONS

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IT HAS been assumed[1, 2] that the plasma volume remains relatively constant with dehydration because it is protected by the much larger extracellular fluid volume. Using improved techniques for measurement of the plasma volume, however, it has been found that considerable decreases in the plasma volume may be associated with dehydration induced in animals by removal of intestinal fluid[3] or the intraperitoneal injection of glucose,[4] and in man by diabetic acidosis[5] and the administration of ammonium chloride.[6]

There is considerable variation of opinion concerning the mode of action and the effectiveness of mercurial diuretics in different diseases because of the variability in the diuretic response from patient to patient as well as in a single patient. When edema is present, it is difficult to evaluate the role played by diuretic drugs because of the spontaneous variations in the pathologic process. In general, it may be said that the diuretic response in patients with heart failure is roughly proportional to the amount of edema.[7]

There is little information[8] concerning the action of mercurial diuretics on normal subjects, and, consequently, there is no standard upon which diuresis may be evaluated. Occasionally, these diuretics are administered to patients who no longer exhibit clinical evidence of edema, and, when diuresis results, it may be interpreted as evidence of "subclinical edema."

These observations were made on normal subjcts in an effort to establish a base line by which the diuretic effect of a single dose of one organic mercurial compound might be evaluated, and to assay the effect of this type of dehydration upon the plasma volume.

METHODS

Ten patients in good health, who were free from cardiovascular or renal disease and had never had edema, were selected as normal subjects for study. Each subject had been on the routine hospital diet, with fluid and salt ad lib., for several days before the observations, and was presumably in a "normal state of hydration."

On the day the observations were started, the subject was weighed in the rested, postabsorptive state on a beam balance which was accurate to

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2 grams. After the weighing, he was placed on a table, and blood samples were taken for determination of the plasma volume,[9] hematocrit,[10] and serum proteins.[11] After forty-five minutes on the table, estimations of the arterial and venous blood pressures[12] were made, and, at the conclusion of the observations, 2 c.c. of mercupurin were injected, intravenously. During the day, the patient was allowed fluids ad lib. and consumed all the food on his trays. The following morning the subject was again weighed, and the observations were repeated while he was in the rested, postabsorptive state.

If the subject consumes his usual diet, changes in weight from one day to the next will reflect closely changes in the water content of the body. It can, therefore, be assumed that the weight lost twenty-four hours after an injection of mercupurin closely approximates the diuresis produced. The error of such an assumption is of little significance in dealing with the large changes in weight which were observed.

Control determinations of the plasma volume and hematocrit were repeated twenty-four times on successive mornings on twenty-two normal subjects. There was a mean difference between the determinations of plasma volume of $+27.5 \pm 19.1$ c.c., or $+0.95 \pm 0.64$ per cent of the initial volume, and a mean percentage change in the hematocrit of -0.75 ± 0.52. In thirteen repeated determinations of the total serum protein, there was a mean percentage change of -0.60 ± 1 per cent.

RESULTS

All subjects experienced a diuresis, and in every case there was a fall in the plasma volume, associated with an increase in the hematocrit reading and serum protein concentration. The changes in plasma volume, serum protein concentration, hematocrit, venous pressure, and body weight are presented in Table I. The percentage change expresses the variations in plasma volume for the group more accurately than the actual change, for the plasma volume will vary considerably with the size of the subject.

Although all of the subjects had a diuresis, there was considerable variation in the degree of response. The average weight loss was 1.73 ± 0.3 kg., or 2.64 ± 0.5 per cent of the body weight. Two subjects, No. 2 and No. 10, had a 3.5 kg. weight loss, while two others lost only 0.5 and 0.7 kg., respectively. The larger subjects underwent a greater change in weight than the smaller ones.

The fall in plasma volume was roughly proportional to the extent of diuresis. The average decrease in the plasma volume was 544 ± 87.7 c.c., or -15.7 ± 2.4 per cent of the initial plasma volume. In two cases, No. 7 and No. 9, the change in the plasma volume was small, and in each instance the diuresis was considerably below the average for the group. The percentage increase in serum protein concentration and hematocrit was considerably less than the decrease in plasma volume. The average change in serum proteins was $+0.74 \pm 0.14$ Gm., or $+11.5 \pm 2.6$ per cent. There was a mean increase in the packed cells of the hematocrit of 2.9 ± 0.6, which represented a mean percentage change of only $+6.9 \pm 1.8$.

TABLE 1

CHANGES TWENTY-FOUR HOURS AFTER THE ADMINISTRATION OF 2 C.C. OF MERCUPURIN TO TEN NORMAL SUBJECTS

CASE	CHANGE IN PLASMA VOLUME (C.C.)	CHANGE IN PLASMA VOLUME (%)	CHANGE IN TOTAL PROTEIN CONCENTRATION (GM.)	CHANGE IN TOTAL PROTEIN CONCENTRATION (%)	CHANGE IN HEMATOCRIT	CHANGE IN HEMATOCRIT (%)	CHANGE IN BODY WEIGHT (KG.)	CHANGE IN BODY WEIGHT (%)	SYSTOLIC BLOOD PRESSURE BEFORE MERCUPURIN	SYSTOLIC BLOOD PRESSURE AFTER MERCUPURIN	DIASTOLIC BLOOD PRESSURE BEFORE MERCUPURIN	DIASTOLIC BLOOD PRESSURE AFTER MERCUPURIN	CHANGE IN VENOUS PRESSURE (MM. SALINE)
1	-580	-20.2	+1.56	+26.5	+3.8	+ 6.5	-1.2	-1.8	120	108	84	86	-25
2	-820	-21.5	+1.08	+17.5	+1.4	+ 2.9	-3.5	-4.5	130	112	84	88	-11
3	-350	- 9.9	+0.77	+11.2	+3.0	+ 7.3	-1.5	-2.5	116	90	70	72	-17
4	-490	-14.0	+0.59	+ 9.0	+1.9	+ 4.5	-0.5	-1.0	120	110	82	84	-38
5	-880	-28.1	+0.72	+10.1	+2.1	+ 4.4	-2.0	-2.7	114	110	80	92	-25
6	-790	-19.5	+0.31	+ 4.6	+1.0	+ 2.4	-0.9	-1.4	105	100	74	82	-18
7	-180	- 6.1	+0.60	+ 9.8	+2.7	+ 5.8	-0.7	-0.9	120	120	84	86	- 5
8	-520	-13.1	+0.30	+ 3.5	+6.5	+18.0	-2.7	-4.3	100	100	76	86	-45
9	- 70	- 3.5	--	--	+0.3	+ 0.8	-0.9	-1.7	90	92	70	70	- 5
10	-760	-21.2	--	--	+6.0	+16.7	-3.5	-5.6	110	105	70	90	-63
Mean	-544	-15.7	+0.74	+11.5	+2.9	+ 6.9	-1.73	-2.64	112.6	104.8	77.4	83.6	-25.2
S.D.	263	7.3	0.37	6.9	1.9	5.5	1.0	1.5	9.7	7.7	6.3	6.4	16
S.E.	±87.7	± 2.4	±0.14	± 2.6	±0.6	± 1.8	±0.3	±0.5	± 3.2	± 2.6	±2.1	±2.1	±5.3

Accompanying the diuresis there was a fall in the venous pressure in every case; in some instances this was quite striking, whereas in others it was of little significance. There was an average decrease of 25.2 ± 5.3 mm. of saline from the control determination. The control venous pressure measurements were all normal, ranging from 70 to 136 mm. of water. There was no significant relationship between the control level of venous pressure and the degree of change. The changes that were most pronounced occurred in Cases 4, 8, and 10, in which the control venous pressures were 78, 120, and 100 mm. saline, respectively. In general, the fall in venous pressure roughly paralleled the decrease in plasma volume and body weight. There was also a significant decrease in the pulse pressure, with a rise in the diastolic pressure and a fall in systolic pressure.

The majority of the subjects observed no change in their state of well-being except some increase in lassitude. A few noted a sensation of weakness and tiredness in the supine position, with dizziness and light-headedness on standing. This was particularly evident in Cases 1, 5, and 10.

DISCUSSION

There are many conflicting reports in the literature concerning the changes in the plasma volume after giving mercurial diuretics. This conflict is probably the result of deductions drawn from slight variations in the constituents of the plasma, from differences in the time the observations were made, and, possibly, from different types of experimental material.

Many investigators have used alterations in the concentration of serum proteins as an index of change in plasma volume. Some[13] reported decreases in the plasma protein concentration shortly after the injection of a mercurial diuretic, followed later, in some instances, by a rise in the plasma protein. Others[14] observed no decrease in the plasma protein, but a consistent increase in its concentration during and after the period of diuresis. Studies based on techniques that measure the plasma volume directly also are in disagreement. Feher[15] found that there was an elevation of the plasma volume either at the height of the diuresis or after diuresis. Brown and Rowntree[16A] and Swigert and Fitz[16B] found changes in the blood volume in either direction. Goldhammer, et al.,[17A] Evans and Gibson,[17B] Calvin and Decherd,[17C] and Herrmann and Decherd[17D] reported that consistent decreases in the plasma volume were present with the onset of diuresis and at the completion of diuresis.

The changes in protein concentration and plasma volume have been used to support theories concerning the action of mercurial diuretics. The demonstration of a decrease in plasma protein concentration and an increase in plasma volume is used to support the theory that these drugs act on the tissues and mobilize tissue fluid. The observers who found increases in protein concentration and decreases in plasma volume consider that these changes are evidence of direct action of the mercurial diuretics on the kidney. This view receives strong support from the work of Goverts,[18] Christian and Bartram,[19] Herrmann, et al.,[20] and Blumgart et al.,[7, 8] who have approached the problem in a different manner. If the action of mercurials is directly on the kidneys, presumably through diminished tubular absorption as the preponderance of more recent work would suggest, then the plasma volume should fall as tubular absorption is impaired, unless it is completely protected by the extracellular fluid. There would appear to be no reason to expect an increase in plasma volume under these circumstances unless protein were added to the blood stream, as suggested by Nonnenbruch. There is no evidence, however, that protein is added to the blood stream; it may actually be lost in certain instances.[21, 22]

The results reported here cannot answer the question whether there are shifts in the plasma volume before or at the time of diuresis. The measurement of plasma volume twenty-four hours after the injection of mercupurin will reflect only the end result of the diuresis. As such, however, there appears to be no suggestion that hydremia has occurred. It is also evident that the plasma volume is not well supported by the extracellular fluid volume.

If the action of mercurial diuretics is directly on the kidney, it might be expected that the plasma volume of normal subjects would suffer greater changes in proportion to the fluid lost than that of an edematous subject, which is presumably supported by a larger volume of extra-

cellular fluid. This may, in part, explain the inconsistent results of Swigert and Fitz [16B] and others who studied edematous patients. It does not explain an increase in the plasma volume after diuresis, and this did not occur in the cases reported here.

Blumgart, et al.,[8] in a careful balance study of two normal subjects who were undergoing salyrgan diuresis, calculated that 90 per cent of the water lost under these circumstances comes from the extracellular fluid, and only 10 per cent from the tissues. The results in these ten subjects indicate that the decrease in plasma volume contributes greatly to the weight lost. The loss of plasma volume would account for 39.6 ± 9.5 per cent of the decrease in body weight. In Cases 4 and 6, the decrease in plasma volume accounted for nearly all of the change in body weight. If these cases are eliminated, the change in plasma volume in the remaining eight cases accounts for 26.3 ± 3.8 per cent of the weight lost. This is in striking contrast to the effect of ammonium chloride diuresis in a similar group of normal subjects,[6] in which the decrease in plasma volume accounted for only 12.2 ± 1.2 per cent of the weight lost.

It is interesting that the average diureses observed in this group of normal subjects after 2 c.c. of mercupurin, namely, 2.6 per cent of the body weight, was less than that which occurred in a similar group on a low-salt diet and ammonium chloride;[6] the latter had an average diuresis of 4.4 per cent of the body weight after a three- or four-day period. Ordinarily, patients with edema do not have a greater diuresis with ammonium chloride than with mercupurin. This discrepancy in these normal subjects may be explained by the fact that, with ammonium chloride, water is lost from both fluid compartments in nearly equal amounts,[23] whereas, with mercupurin, water is lost largely from the extracellular fluid compartment. Thus, in the absence of abnormal accumulations of extracellular fluid, ammonium chloride administration might be expected to produce a greater weight loss.

These results suggest that a normal subject may have a diuresis of 2 to 6 pounds, or 1 to 4 per cent of the body weight, in response to a 2 c.c. injection of mercupurin. At times, after a patient has recovered from congestive heart failure, diuretics are still used when there is no longer clinical evidence of edema. When a diuresis of six pounds or less occurs in such cases, it should not necessarily be interpreted as evidence of abnormal accumulations of edema fluid, and should suggest that further diuresis may not be necessary. Such a diuresis should not be interpreted as evidence of "subclinical edema." Furthermore, the administration of mercurial diuretics to such patients may produce severe dehydration and the clinical picture characterized by weakness, apathy, delirium, and, at times, unconsciousness, described by Poll and Stern.[24]

The failure of the concentration of serum protein and the hematocrit readings to increase in proportion to the fall in plasma volume under these circumstances has been noted before.[25] This again is evidence that shifts in these components fail to reflect quantitatively the change in plasma volume, although they may indicate that the plasma volume is undergoing changes, and the direction of the change.

The consistent fall in the venous pressure in these cases appears to be related to the decrease in plasma volume and body weight. Large changes in the plasma volume, with two exceptions, Cases 2 and 6, were accompanied by pronounced changes in the venous pressure. Since the veins of the forearm are a series of collapsible tubes, the pressure in them is dependent upon the pressure of the surrounding tissues,[25] the intrathoracic pressure,[28] and the pressure in the right auricle.[27] Ryder, Molle, and Ferris[26] have indicated that the pressure in a peripheral vein in normal subjects is a function of tissue pressure causing collapse of that vein along its course to the heart, so that it is independent of the auricular pressure. Richards, et al.,[27] found a gradient of 39 mm. of water between the antecubital venous pressure and the auricular pressure in nine normal subjects. The gradient tends to disappear as the pressure in the auricle rises in congestive heart failure. The pressure in the peripheral veins is not changed by decreases in the intrathoracic pressure below normal, but will be affected by increased intrathoracic pressure.[28] Another factor, however, must be considered in evaluating the decrease in venous pressure. Warren and Stead[29] found that, with pooling of blood in the lower extremities of six normal subjects, there was a fall in the antecubital venous pressure of 23 mm., and, in the external jugular pressure, of 53 mm. Under these circumstances, the decrease in the amount of blood returning to the auricle was the chief factor affecting the venous pressure, and it would appear that either the volume of blood flow or the auricular pressure, or both, had some effect on the peripheral venous pressure.

The fall in venous pressure after the injection of mercupurin may be explained by several factors. The loss of extracellular fluid in the tissues surrounding the antecubital vein may result in a decrease in tissue pressure. In these cases, the weight loss was relatively small, and it appears unlikely that this factor would be of great importance. The decrease in arterial pulse pressure and the symptoms of weakness and apathy at rest in bed and dizziness and faintness in the upright position experienced by some of these subjects suggest that there was a decrease in the blood flow. This might produce the fall in venous pressure as a result of the decreased filling of the vascular bed in the region of the antecubital vein, thereby decreasing the tissue tone. The decrease in blood flow, if present, may be the result of a decrease in the auricular pressure associated with the lower plasma volume, which may be reflected by the fall in the antecubital venous pressure. The failure to demonstrate more consistent changes in the venous

pressure under these circumstances may be the result of individual variation in the degree of local obstruction to the flow of blood in the antecubital vein, which thus masks changes in the auricular pressure.

The symptoms exhibited by some of these normal subjects are similar in many respects to those noted by edematous subjects after extensive diuresis,[24] and suggest that diminishing blood volume may play an important role. The clinical picture of apathy, weakness, delirium, and unconsciousness after extensive diuresis and the symptoms associated with a diminished blood volume which were noted by the normal subjects are analogous, in many ways, to the clinical appearance and circulatory defect of shock.

SUMMARY

1. Plasma volume, serum protein concentration, hematocrit value, arterial and venous blood pressures, and body weight were determined in ten normal subjects before, and twenty-four hours after, the injection of 2 c.c. of mercupurin.

2. There was a fall in plasma volume in every case, averaging 544 ± 87.7 c.c., or 15.7 ± 2.4 per cent of the control determination; an average rise in serum proteins of 0.74 ± 0.14 Gm., or 11.5 ± 2.6 per cent; and an average rise in hematocrit of 2.9 ± 0.6, or 6.9 ± 1.8 per cent.

3. A diuresis was experienced in every case; the mean was 1.73 ± 0.3 kg., or 2.6 ± 0.5 per cent of the body weight.

4. Associated with the diuresis and decrease in plasma volume, there was a fall in venous pressure and pulse pressure.

5. In some instances, the subjects exhibited weakness, apathy, dizziness, and faintness, suggesting a diminution in cardiac output.

REFERENCES

1. Gamble, J. L., and McIver, M. A.: Body Fluid Changes Due to Continued Loss of the External Secretion of the Pancreas, J. Exper. Mer. **48**: 859, 1928.
2. Gamble, J. L.: Extracellular Fluid: Extracellular Fluid and Its Vicissitudes, Wm. Sydney Thayer and Susan Read Thayer Lecture, Bull. Johns Hopkins Hosp. **61**: 151, 1937.
3. Mellors, R. C., Muntweyler, E., Mautz, F. R., and Abbott, W. E.: Changes of the Plasma Volume and "Available (Thiocyanate) Fluid" in Experimental Dehydration, J. Biol. Chem. **144**: 785, 1942.
4. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determination of Plasma Volume With T 1824, and "Available Fluid" Volume With Sodium Thiocyanate, Am. J. Physiol. **125**: 142, 1939.
5. Jacobson, S. D., and Lyons, R. H.: Changes in Blood Volume Produced by Diabetic Acidosis, J. Lab. & Clin. Med. **27**: 1169, 1942.
6. Lyons, R. H., Jacobson, S. D., and Avery, N. L.: The Effect on the Plasma Volume of Dehydration Produced by a Low-Salt Diet and Ammonium Chloride, AM. HEART J. **27**: 353, 1944.
7. Blumgart, H. L., Gilligan, D. R., Levy, R. C., and Brown, M. G.: The Effect of Diuretics on Water and Salt Metabolism, Tr. A. Am. Physicians **47**: 304, 1932.
8. Blumgart, H. L., et al.: Action of Diuretic Drugs, I: Action of Diuretics in Normal Persons, Arch. Int. Med. **54**: 40, 1934.
9. Gibson, J. G., Jr., and Evelyn, K. A.: Clinical Studies of Blood Volume; Adaptation of Method to a Photoelectric Microcolorimeter, J. Clin. Investigation **17**: 153, 1938.

10. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte, J. Lab. & Clin. Med. **17**: 899, 1932.
11. Barbour, H. G., and Hamilton, W. F.: Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**: 625, 1926.
12. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: The Measurement of Venous Pressure by the Direct Method, AM. HEART J. **16**: 675, 1938.
13. A. Saxl, P., and Heilig, R.: a. Ueber die diuretische Wirkung von Novasurol und anderen Quicksilberinjectionen, Wien. klin. Wchnschr. **33**: 943, 1920. b. Über die Novasuroldiurese, Ztschr. f. d. ges. exper. Med. **38**: 94, 1923.
B. Crawford, J. H., and McIntosh, J. F.: Observations on the Use of Novasurol in Edema Due to Heart Failure, J. Clin. Investigation **1**: 333, 1925.
C. Bohn, H.: a. Experimentelle Studien über die diuretische Wirkung des Novasurols, Ztschr. f. d. ges. exper. Med. **31**: 303, 1923. b. Fortgesetzte Studien über Novasurol, seine Wirkung bei verschiedenen Lebensaltern und bei Diabetikern, sowie sein etwaiger. Einfluss auf Ionenverscheibungen in Organismus, Deutsches Arch. f. klin. Med. **143**: 225, 1923.
D. Claussen, F.: Über die Diurese der Herzkranken, Ergebn. d. inn. Med. u. Kinderh. **43**: 764, 1932.
E. Meyer, P.: Untersuchungen über den kolloidosmotischen Druck des Blutes II Die Salyrgandiurese, Ztschr. f. Klin. Med. **116**: 174, 1931.
F. Kylin, E.: Studien über den Kolloidosmotischen (onkotischen) Druck XVIII Über die Einwirkung verschiedener Diuretika auf den kolloidosmotischen Druck, Arch. f. exper. Path. u. Pharmakol. **164**: 33, 1932.
G. Serby, A. M.: The Pharmacology and Therapeutics of Novasurol, Arch. Int. Med. **38**: 374, 1926.
14. A. Nonnenbruch, W.: Über die Wirkung des Novasurols auf Blut und Diurese, München. med. Wchnschr. **68**: 1282, 1921.
B. Oelkers, H. A.: Untersuchungen über den Kolloidosmotischen Druck des Serums, Ztschr. f. klin. Med. **115**: 854, 1931.
C. Schmitz, H. L.: Studies on the Action of Diuretics I: The Effect of Euphyllin and Salyrgan Upon the Glomerular Filtration and Tubular Reabsorption, J. Clin. Investigation **11**: 1075, 1932.
Studies on the Action of Diuretics II: The Effect of Salyrgan on the Water Content of the Plasma as Measured by the Refractive Index, J. Clin. Investigation **12**: 741, 1933.
D. Bryan, A. H., Evans, W. A., Fulton, M. N., and Stead, E. A., Jr.: Diuresis Following the Administration of Salyrgan, Arch. Int. Med. **55**: 735, 1935.
15. Feher, S.: Salyrgandiurese und zirkulierende Blutmenge, Wien. klin. Wchnschr. **42**: 964, 1929.
16. A. Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood and Changes Incident to Diuresis in Cases of Edema, Arch. Int. Med. **35**: 129, 1925.
B. Swigert, V. W., and Fitz, R.: The Effect of Mersalyl (Salyrgan) on the Plasma Volume, J. A. M. A. **115**: 1786, 1940.
17. A. Goldhammer, S., Leiner, G., and Scherf, D.: Über die zerkulierende Blutmenge vor und nach der Quecksilberdiurese, Klin. Wchnschr. **14**: 1109, 1935.
B. Evans, W. A., Jr., and Gibson, J. G.: The Blood Volume in Diuresis, Am. J. Physiol. **118**: 251, 1937.
C. Calvin, D. B., Decherd, G., and Herrmann, G.: Response of Plasma Volume to Diuretics, Proc. Soc. Exper. Biol. & Med. **44**: 529, 1940.
D. Herrmann, G., Decherd, G. M., and Calvin, D. B.: The Application of Blood Volume Studies to the Theory of the Mechanism of Diuresis, Tr. A. Am. Physicians **56**: 298, 1941.
18. Goverts, P.: Origine renale ou tissulaire de la diurèse par und composé Mercurial organique, Compt. rend. Soc. de biol. **99**: 647, 1928.
19. Christian, H. A., and Bartram, E. A.: Experimental Observations on the Action of Diuretics, Tr. A. Am. Physicians **47**: 292, 1932.
20. Herrmann, G., et al.:
A. Some Studies in the Mechanism of Diuresis in Patients With Congestive Heart Failure, Tr. A. Am. Physicians **47**: 279, 1932.
B. Further Studies on the Mechanism of Diuresis in Patients With Congestive Heart Failure, Tr. A. Am. Physicians **48**: 364, 1933.
C. Herrmann, G., and Decherd, C.: Further Studies on the Mechanism of Diuresis With Especial Reference to the Action of Some Newer Diuretics, J. Lab. & Clin. Med. **22**: 767, 1937.
21. Calvin, D. B., Decherd, G., and Herrmann, G.: Plasma Protein Shifts During Diuresis, Proc. Soc. Exper. Biol. & Med. **44**: 529, 1940.

22. Lyons, R. H., Jacobson, S. D., and Neerken, A. J.: To be published.
23. A. Gamble, J. L., Blackfan, K. D., and Hamilton, B.: A Study of Diuretic Action of Acid Producing Salts, J. Clin. Investigation **1**: 359, 1925.
B. Følling, A.: On the Mechanism of the Ammonium Chloride Acidosis, Acta med. Scandinav. **71**: 221, 1929.
C. Loeb, R. F., et al.: On the Mechanism of Nephrotic Edema, J. Clin. Investigation **11**: 621, 1932.
D. Wiley, F. H., Wiley, L. L., and Waller, D. S.: The Effect of the Ingestion of Sodium Potassium and Ammonium Chlorides and Sodium Bicarbonates on the Metabolism of Inorganic Salts and Water, J. Biol. Chem. **101**: 73, 1933.
24. Poll, D., and Stern, J. E.: Dangers of Dehydration Treatment in Heart Disease, M. Clin. North America **21**: 1873, 1937.
25. A. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, Am. J. Physiol. **132**: 411, 1941.
B. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That the Cell Plasma Ratio of Blood Contained in Minute Vessels Is Lower Than That of Venous Blood, J. Clin. Investigation **20**: 317, 1941.
C. Stewart, J. D., and Rourke, G. M.: Changes in the Blood and Interstitial Fluid Resulting From Surgical Operation and Ether Anesthesia, J. Clin. Investigation **17**: 413, 1938.
D. Mellors, R. C., Muntweyler, E., Mautz, F. R., and Abbott, W. E.:[3]
E. Lyons, R. H., Jacobson, S. D., and Avery, N. L.:[6]
F. Calvin, D. B., Decherd, G., and Herrmann, G.:[21]
26. Ryder, H. W., Molle, W. E., and Ferris, E. B., Jr.: The Significance of the Peripheral Venous Pressure, Proc. Central Soc. Clin. Research **14**: 44, 1941.
27. Richards, D. W., Jr., Cournand, A., Darling, R. C., and Gillespie, W. H.: Pressure in the Right Auricle of Man in Normal Subjects, and in Patients With Congestive Heart Failure, Tr. A. Am. Physicians **56**: 218, 1941.
28. Holt, J. P.: The Collapse Factor in the Measurement of Venous Pressure, Am. J. Physiol. **134**: 292, 1941.
29. Warren, J. V., and Stead, E. A., Jr.: The Effect of the Accumulation of Blood in the Extremities on the Venous Pressure of Normal Subjects, Am. J. M. Sc. **205**: 501, 1943.