MECHANISM OF DIURESIS: ALTERATIONS IN THE SPECIFIC GRAVITY OF THE BLOOD PLASMA WITH ONSET OF DIURESIS IN HEART FAILURE

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There are divergent views concerning the mechanism by which diuresis is initiated. Many of the observations on this subject relate to mercurial drugs. Crawford and McIntosh (1) concluded that novasurol induced primary dilution, followed by concentration of the blood in edematous patients. Bryan, Evans, Fulton, and Stead (2) thought that salyrgan resulted in concentration of the blood, since sustained rise in its specific gravity occurred coincident with diuresis in dogs made edematous by plasmapheresis. Schmitz (3) did not find evidence that salyrgan mobilized fluid into the blood stream before the onset of diuresis. Blumgart, Gilligan, Levy, Brown, and Volk (4) concluded from observations on normal subjects that diuresis following xanthine and mercurial drugs was not initiated by the kidneys in response to measurable changes in specific gravity or sodium or chloride contents of the blood. Brown and Rowntree (5) found an increase in blood volume with the onset of diuresis in cardiac patients. On the other hand, using more accurate methods, Evans and Gibson (6) observed in dogs a diminution of plasma volume during diuresis induced by salyrgan.

For purposes of analysis the circulatory-renal system consists of the kidneys on the one hand and the tissues which retain fluid on the other, the circulating blood connecting them. Tissue fluid to be excreted as urine must be carried by the blood to the kidneys. The stimulus to inaugurate diuresis may be applied at different points in this system. If the mechanism is initiated in the kidneys and increased secretion of urine is the first step, concentration of the blood should occur on the withdrawal of fluid from it. How far this imbalance in the blood constituents can proceed and how long it can be present before restoration occurs by the entrance of fluid from the edematous tissues might vary with different diuretics. Moreover, its duration may be brief before restoration is attempted, or it may be long enough and of such magnitude that it can be detected.

On the other hand, if diuresis is initiated at the tissue side of the system so that fluid enters the blood stream first, dilution of the blood would occur. Equilibrium would be disturbed until the kidneys began to excrete the surplus fluid. If dilution of the blood was of sufficient duration and magnitude, it might be detected.

It appeared that frequent observations of the specific gravity of the blood would reflect changes in dilution and concentration of the blood and give data which would contribute to one or the other of these points of view. Moore and Van Slyke (7) demonstrated a linear relationship between the observed specific gravity of the plasma of the blood and the observed protein content of the plasma of normal individuals and nephritic patients. They found also that when the specific gravity of the plasma was below 1.0223 in certain types of nephritis, edema was present, and that when the specific gravity was above this level, the so-called edema zone, edema did not occur.

In cardiac patients, Moore and Stewart (8) also found that the specific gravity of the plasma had a linear relationship to the protein content of the plasma and demonstrated that the plasma proteins and specific gravity of cardiac patients were above the edema level of nephritic patients. Moore and Stewart's (8) observations relating to the behavior of the specific gravity of the plasma of normal individuals provided the background for turning Moore and Van Slyke's method to this purpose. They found that the specific gravity of the blood plasma of normal individuals and of cardiac patients in water equilibrium remained constant to within 0.0004 from day to day. Dilution of blood by the injection of normal salt solution and following hemorrhage in dogs gave paral-

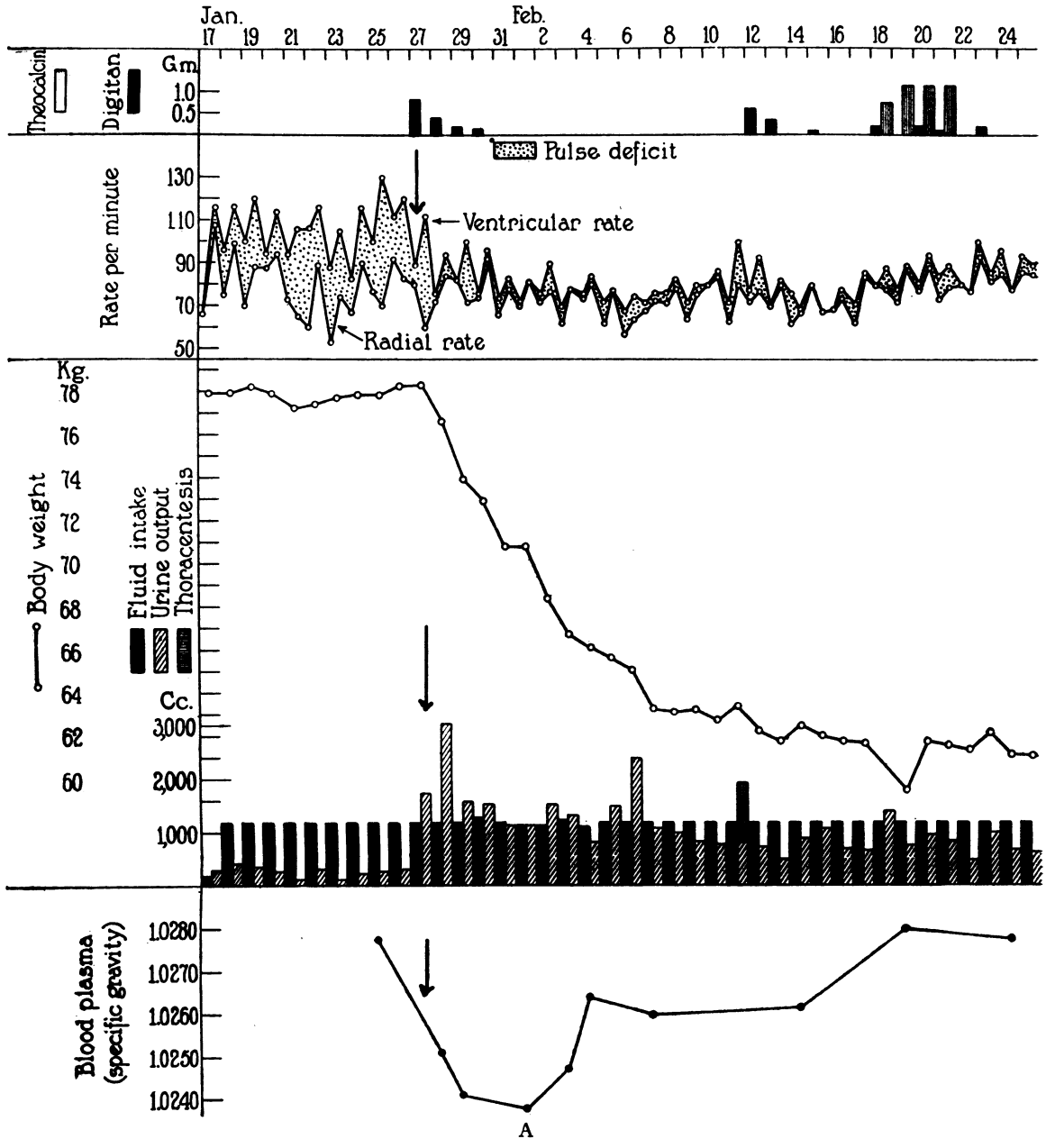

FIG. 1. RELATIONSHIP BETWEEN ONSET OF DIGITALIS, THEOCALCIN, AND SPONTANEOUS DIURESIS TO SPECIFIC GRAVITY OF THE BLOOD PLASMA

In this figure is shown the relation of onset of diuresis to the level of specific gravity of the blood plasma. In B. McL., 58 years (Figure 1*A*), in whom heart failure was a consequence of hypertension, diuresis resulted from giving digitan 1.2 grams in 24 hours. In L. C., 64 years (Figure 1*B*), in whom heart failure resulted from hypertension, the administration of theocalcin 4.5 grams on April 14, and daily thereafter, resulted in marked diuresis. In J. McM., 44 years (Figure 1*C*), in whom heart failure resulted from arteriosclerotic heart disease, diuresis occurred spontaneously.

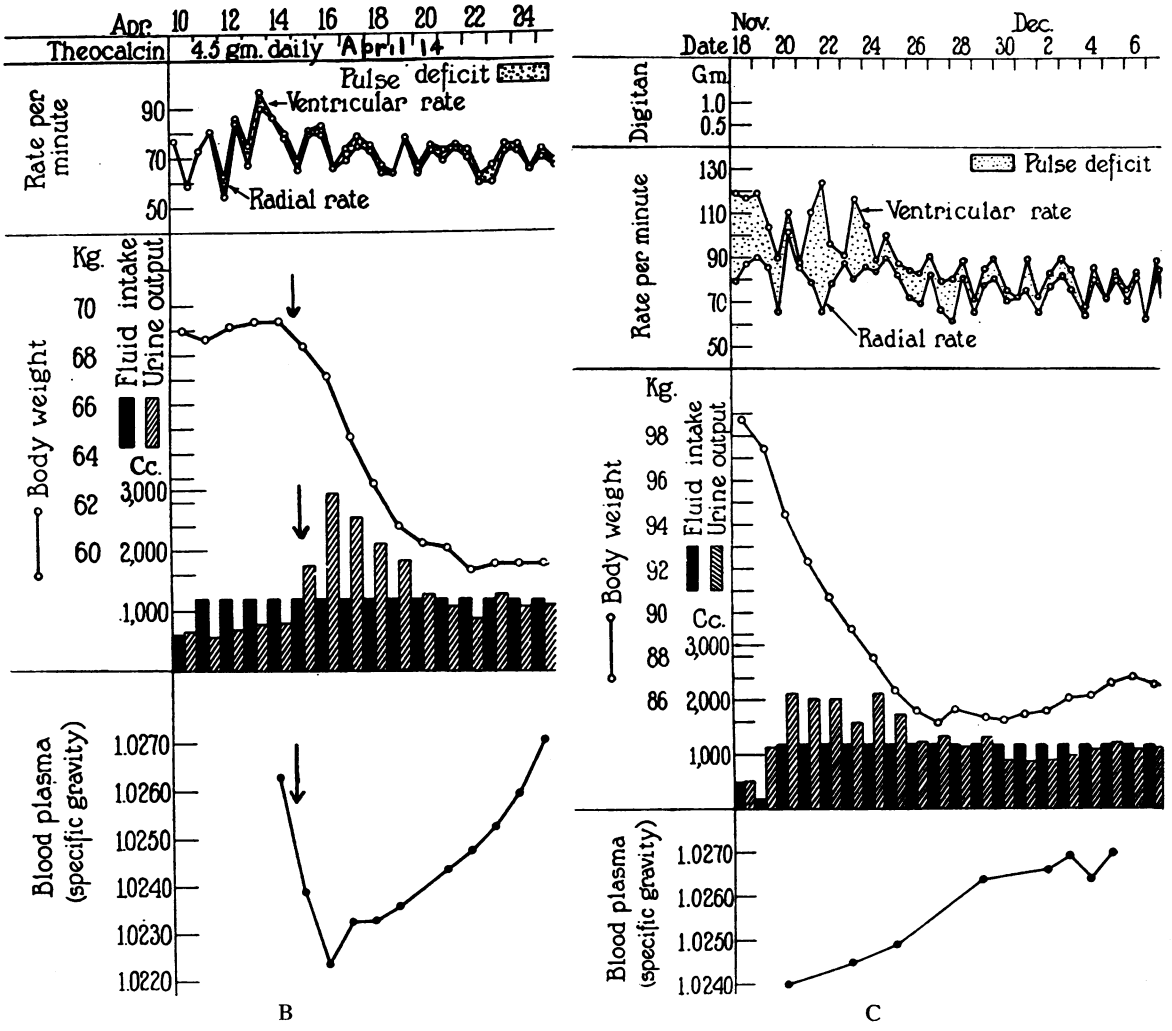

FIG. 1 (*continued*)

lel decreases in specific gravity of the plasma and plasma proteins. The oral administration of 1000 cc. of water did not alter specific gravity of the plasma; during the urine concentration test, however, the specific gravity and the plasma proteins increased, indicating concentration of the blood. In short, when concentration of the blood occurs, the specific gravity rises and when dilution occurs, it decreases.

It appeared from these observations that during a time in which nothing was done to deplete the plasma proteins, the specific gravity of the plasma could be used to indicate dilution or concentration of the blood.

METHODS AND PLAN OF OBSERVATIONS

The specific gravity of the plasma of the blood of cardiac patients exhibiting signs and symptoms of congestive heart failure was estimated by the method of Moore and Van Slyke (7). Duplicate samples were checked to within 0.00002. The daily fluid and salt intakes of the patients were 1200 cc. and 5 grams, respectively. Patients remained in bed. There was a control period before giving diuretics. Since samples of blood were taken frequently before and after the administration of diuretics, it was not expedient to keep the subjects in the basal or postabsorptive state. The patients ate breakfast at 7:30 a.m., after which they received no fluid[1] until samples of blood were taken without stasis at 10:30 a.m. The diuretic was then given. A rubber stopper was used to eliminate evaporation. Clotting was prevented by use of heparin.

[1] It is recalled, however, that Moore and Stewart (8) found that drinking 1000 cc. water did not alter the specific gravity of the blood.

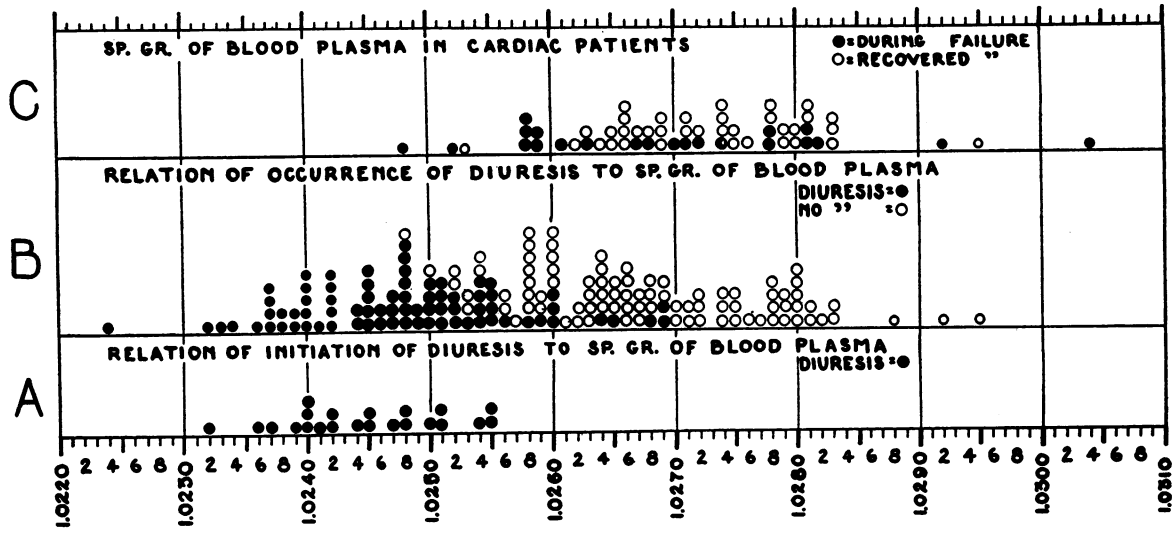

FIG. 2. RELATION OF INITIATION AND OCCURRENCE OF DIURESIS TO SPECIFIC GRAVITY OF THE BLOOD PLASMA

In Figure 2*A* are plotted specific gravity estimations of the plasma to show the level at which diuresis was initiated. Closed circles indicate that diuresis was initiated at the level shown. In Figure 2*B* are plotted data to show the relation of occurrence and persistence of diuresis to specific gravity of the blood plasma. Closed circles indicate occurrence of diuresis and open ones that diuresis was not taking place. In Figure 2*C* are plotted specific gravity estimations of patients during (closed circles) and recovered (open circles) from heart failure.

OBSERVATIONS

Specific gravity of the blood plasma was observed in instances of diuresis occurring spontaneously without the use of drugs (8 patients), in diuresis resulting from digitalis (9 patients), and, finally, in diuresis following the use of theocalcin (Merck) (5 patients). Patients having auricular fibrillation, as well as those with normal sinus rhythm, were subjects.

Patient B. McL. (Figure 1*A*) illustrates the effect of digitalis. Rest in bed and restriction of fluids did not result in diuresis. When digitan 1.2 grams (Merck) [2] were given in 24 hours, diuresis with loss in weight occurred promptly. The ventricular rate decreased. On the first day of diuresis, the specific gravity of the blood plasma fell to 1.0250 from a control level of 1.0280, and the next day, with further increase in urine output, to 1.0230, and then rose gradually to 1.0280 again. Similar results were seen in 7 patients with auricular fibrillation and in 2 patients with normal sinus rhythm. In an eighth patient with auricular fibrillation, in whom diuresis did not occur, specific gravity of the plasma did not fall.

The case of L. C. (Figure 1*B*) illustrates the effect of theocalcin. The specific gravity of the plasma was 1.0264 during the control period; with 4.5 grams of theocalcin daily, diuresis occurred promptly; the specific gravity fell immediately to 1.0239 and then further the next day to 1.0223 and rose gradually to 1.0275 toward the end of diuresis. Similar patterns were recorded in one other patient with auricular fibrillation and 3 patients with normal sinus mechanism.

The case of J. McM. (Figure 1*C*) illustrates the results in 3 patients with auricular fibrillation and 5 patients with normal sinus rhythm in whom diuresis occurred spontaneously with rest in bed and limitation of fluid intake. There was a fall in specific gravity when diuresis occurred; or, if diuresis had been initiated when the first sample was taken, the specific gravity was low, rose with the continuance of diuresis, and had risen to a normal level when excess fluid had been eliminated.

For all patients the level of specific gravity of the plasma was plotted to show the *onset* of diuresis (Figure 2*A*). When it fell to 1.0250 in 17 instances and to 1.0255 in 5 instances, diuresis was initiated; above 1.0255 the *onset* of diuresis was not observed.

For all patients the level of specific gravity of the blood plasma was plotted to show not only the onset but also the persistence of diuresis (Figure 2*B*) after it had been initiated. *Below 1.0248,* diuresis either occurred or was initiated in *every* instance, and in the zone 1.0248 to 1.0255, there were only a few instances in which diuresis was not occurring. Diuresis, having been initiated at a specific gravity below 1.0255, may continue with a rising specific gravity, even when it has attained values up to 1.0269. The value 1.0255 may be called the critical level for the initiation of diuresis in congestive heart failure.

The specific gravity of the plasma of 13 cardiac patients, in water equilibrium during congestive heart failure, ranged from 1.0248 to 1.0304 (Figure 2*C*). In one subject only it was at this lower level, and in 3 instances

[2] This amount of this preparation decreased the ventricular rate in auricular fibrillation to around 70 per minute when given in 24 hours and was called the digitalizing amount.

only was it below 1.0258. In short, all values were in the normal range and above the edema level of 1.0233 found for patients with nephritis (7). Moreover, these values are above the diuresis level which was observed in patients in this study. The specific gravity of the plasma of 16 cardiac patients, in water equilibrium and recovered from congestive heart failure, ranged from 1.0253 to 1.0295 (Figure *2C*), values similar to those recorded during failure.

DISCUSSION

Data now available show that the specific gravity of the blood plasma of cardiac patients, whether before the occurrence of failure (8), during failure, or after recovery from failure, when the subjects are in water equilibrium, is in the normal range, 1.0248 to 1.0304; the occurrence of edema in them does not depend on the level of specific gravity of the plasma or of the plasma proteins. When theocalcin or digitalis was given and diuresis occurred, the specific gravity of the plasma fell from a higher level to 1.0255 or lower (Figures *1A*, *1B*, *2A*) and, in all except 6 instances, fell below 1.0248. Once diuresis had been initiated, it could proceed with a specific gravity above these levels as the specific gravity returned toward or above the original levels (Figure *2B*). The pattern was similar when diuresis occurred spontaneously. These observations indicate that fluid is drawn into the blood, giving rise to dilution of the blood and by inference to increase in its volume. Since this was the sequence on each occasion when diuresis occurred, the inference may be drawn that increase in blood volume was the stimulus which led the kidneys to begin diuresis. When the specific gravities of frequent samples of blood taken before and after the giving of these drugs were correlated with the voiding of urine, it was observed that a fall in specific gravity of the plasma preceded the occurrence of diuresis. The occurrence of diuresis could be predicted when it was discovered whether the specific gravity fell or was unchanged. In no instance did the specific gravity rise with onset of diuresis.

In patient E. G. the specific gravity of the plasma before the onset of diuresis was 1.0270. The specific gravity of the edema fluid, removed from the legs by Southey tubes and collected under oil to avoid evaporation, was 1.0080. With the initiation of diuresis 3 days later, the specific gravity of the plasma fell to 1.0240. By the addition of varying amounts of edema fluid to the blood plasma and estimation of the specific gravity of the mixture, it was calculated that the addition of approximately 400 cc. of edema fluid having a specific gravity of 1.0080 to the blood would have been sufficient to reduce the specific gravity to the observed level of 1.0240. The blood volume was presumably increased by this amount. Estimation of the urinary excretion of protein in a few patients during diuresis did not account for the low concentration indicated by the fall in specific gravity, and eliminated the possibility that there had been loss of proteins from the blood by this channel. The decrease was thought to be due not to loss of protein from the blood, but to dilution of the blood by edema fluid or by other fluid accumulations. It is to be emphasized that diuresis did not occur because the plasma proteins had been lowered. The fall in specific gravity from a high level to a low one represented increase in blood volume with dilution of the blood; in short, sufficient increase in blood volume had occurred by change from the high specific gravity to 1.0255, or lower, to provide the stimulus for the kidneys to initiate diuresis.

These results, in diuresis occurring spontaneously as well as following digitalis and theocalcin, are similar to those Crawford and McIntosh (1) found with novasurol. They differ, however, from Evans and Gibson's (6) findings in dogs. The divergent results may be due in part to the difference of the subjects in the two studies (patients suffering from heart failure in one, and dogs rendered edematous by plasmapheresis in the other) and in part to different drugs.

The normal level of specific gravity of the plasma in cardiac patients not only during failure but after recovery from failure demonstrates that the occurrence of edema is not dependent upon lowered plasma proteins. These results are in agreement with those of Moore and Stewart (8). On the other hand, Thomson (9), Ellis (10) and Payne and Peters (11) have found low plasma proteins in patients with cardiac edema. The data now being recorded show that the specific gravity of the plasma and the plasma proteins decrease with onset of diuresis. It may be that certain of Thomson's (9) and Ellis' (10) and Payne and Peters' (11) patients were not in water

equilibrium when observations were made; diuresis may have been about to start or was already occurring. Data relating to urine output and changes in body weight were not available in their papers for making an analysis from this point of view. No doubt, in certain cardiac patients plasma protein deficiency from low protein intake or as the result of cardiac cirrhosis may also be operative as an additional factor, but it does not appear to play a rôle in the causation of edema in the uncomplicated case of heart disease with failure.

SUMMARY

(1) Change in level of the specific gravity of the plasma has been used as a measure of change in blood volume, decrease in specific gravity indicating dilution of the blood, and increase in specific gravity concentration. It appeared that diuresis in the presence of heart failure of the congestive type depended on changes initiated in the tissues, since it was accompanied by decrease in specific gravity of the plasma, that is to say, by dilution of the circulating blood with increase in blood volume. Dilution of the blood preceded the onset of diuresis and increase in blood volume appeared to be the stimulus that initiated diuretic response of the kidneys. The results were similar not only when diuresis occurred spontaneously, but when it was occasioned by digitalis and by theocalcin and, moreover, whether in the presence of normal sinus rhythm or of auricular fibrillation, and whether the cause of the heart disease was rheumatic fever, syphilis, arteriosclerosis or hypertension. These studies do not relate to the anatomical portions of the kidney which take part in the accelerated formation of urine in diuresis.

(2) The specific gravity of the plasma must fall from a high level to 1.0255 or lower for the initiation of diuresis. Below this level may be called the diuretic zone in heart failure, in that it corresponds to a dilution of the blood with increase in blood volume of sufficient magnitude to initiate diuresis.

(3) In uncomplicated heart disease the level of specific gravity of the plasma, and by inference the plasma proteins (7, 8), is in the normal range not only before the onset of failure (8) but during and after recovery from failure. Plasma protein deficiency does not participate in the etiology of cardiac edema usually.

(4) In the technique of taking blood for plasma or serum proteins or specific gravity of the plasma, samples should not be obtained when diuresis is being initiated or occurring, since low results may be recorded which do not reflect the usual level for the subject. Results should be interpreted in the light of the effect of diuresis which has been demonstrated in this investigation.

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