Discussion and Summary. These experiments show definitely that carotene administered parenterally may be effectively utilized provided the carotene has been water-solubilized by solution in Tween 80. In such a solution not only is there a much more rapid transport of carotene from the site of an intramuscular injection, but there also occurs an effective conversion to vitamin A as demonstrated by the resumption of growth in vitamin A-depleted rats. These findings offer further support to the accumulating evidence[2,4] that the state of dispersion of the carotene is of importance for participation in the physiological processes of absorption, transport and enzymatic conversion to vitamin A.

3 Tomarelli, R. M., and György, P., *J. Biol. Chem.*, 1945, **161**, 367.

4 Greaves, J. D., and Schmidt, C. L. A., *Am. J. Physiol.*, 1935, **111**, 492.

15515

Alterations in Body Fluids During Acute Infectious Hepatitis.

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It has long been known that convalescence in acute liver disease may be initiated by a diuresis. Jones and Eaton[1] in noting this phenomenon in an unselected group of patients with acute and subacute liver disease suggested that it may have a favorable prognostic significance. To imply that recovery from liver disease is associated with the production of a large volume of urine, suggests that during the acute phase of the infection there may be profound disturbances in water metabolism involving increased water storage and possibly alterations in the transport and excretion mechanisms. Recognition of the intimate relationship existing between hepatic and renal physiology has impelled clinicians to speak of the ill-defined and little understood "hepato-renal syndrome." The suppression of urine volume in "catarrhal jaundice" and acute yellow atrophy are old observations,[2] as is the oliguria accompanying cirrhosis of the liver, especially when associated with ascites.[3] It is conceivable, therefore, that the latter may in part represent a more serious extension of the same mechanism to an advanced period in the development of chronic liver disease. Indeed, recent evidence suggests that the movement of body fluids during liver disease may be under endocrine control.[4] No available data exist that reveal the precise alterations of the fluid compartments of the body during the course of acute liver disease. Jones and Eaton[1] suggested that the observed diuresis of convalescence was a consequence of improved hepatic efficiency, resulting in a "shift of fluid from the tissues or serous cavities to the blood stream with the ultimate establishment of diuresis." Since adequate methods now exist for the simultaneous determination of approximate interstitial fluid (thiocyanate space), plasma volume and total blood volume, it was believed that a study of the distribution of body fluids during the course of acute infectious hepatitis would be of profit. In this disease one may work in a rapidly shifting metabolic scene.

Materials and Methods. Fourteen patients were studied as part of a group of acute infectious hepatitis cases observed in the Rockefeller Hospital.[5] All were young, adult males

* Dr. Hoagland died Aug. 2, 1946.

1 Jones, C. M., and Eaton, F. B., *New Eng. J. Med.*, 1935, **213**, 907.

2 Van Noorden, C., *Pathology*, 1907, **2**, 267.

3 Adler, A., *Klin. Woch.*, 1923, **2**, 1980.

4 Ralli, E. P., Robson, J. S., Clarke, D., and Hoagland, C. L., *J. Clin. Invest.*, 1945, **24**, 316.

5 Hoagland, C. L., and Shank, R. E., *J. A. M. A.*, 1946, **130**, 615.

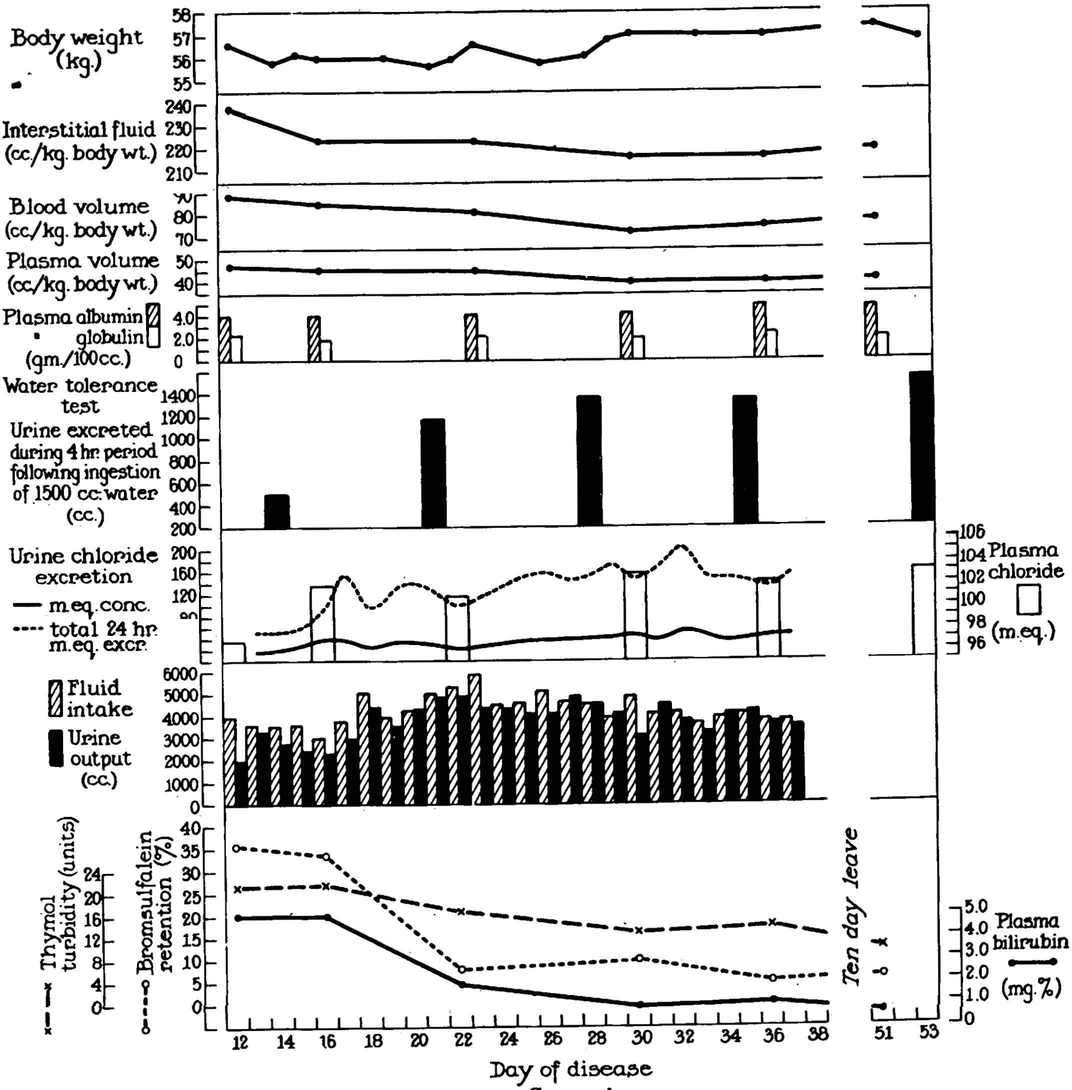

CHART 1.

with previous good health, whose disease course proceeded without complication. In each case, the diagnosis was obtained by a careful history and physical examination and confirmed by appropriate liver function tests. Throughout the study rigid water-balance conditions were maintained. This consisted of the daily determination of body weight and careful measurements of fluid intake and urine output. An attempt was made to keep the diet and salt intake constant for each patient. Measurements of plasma volume and interstitial fluid were determined at 4- to 7-day intervals, according to the simultaneous method of Gregerson and Stewart[6] in which the dye T1824 and sodium thiocyanate measured in the Coleman, Jr. spectrophotometer[7] were used. In this study the interstitial fluid volume was derived by subtracting the plasma volume from the total thiocyanate space. Although this fails to account for the small amount of red blood cell water, there was

6 Gregerson, M. I., and Stewart, J. D., *Am. J. Physiol.*, 1939, **125**, 142.

7 Gibson, J. G., Jr., and Evans, W. A., Jr., *J. Clin. Invest.*, 1937, **16**, 301.

too little change throughout the course of the disease in the red blood cell volume, as measured by the venous hematocrit, to be of significance.[6] Total blood volume was calculated from the plasma volume by means of the venous hematocrit taken on the same sample.[8] The plasma bilirubin was determined according to the method of Malloy and Evelyn adapted to the Coleman, Jr. spectrophotometer.[9] This, together with the bromsulfalein test,[10] measurements of the plasma protein fractions and the thymol turbidity reaction of the serum,[11] were the indices of choice in following the state of liver function at frequent intervals. The total plasma protein and albumin and globulin fractions were determined by the micro-digestion method, in which Nesslerization[12] was used. Normal values for this method are: total protein, 6.0-8.0 g %; albumin, 3.5-5.0 g %; globulin, 1.5-3.0 g %; A/G ratio, 1.5-3.3. Blood specimens for plasma chlorides were collected under oil and measured according to the method of Wilson and Ball.[13] To disclose any tendency to store fluid, a water tolerance test was utilized at weekly intervals.[14] This is a simple expression of the volume of urine excreted under basal conditions in the 4 hours following the rapid ingestion of 1500 cc of water. This test was not performed on the days that the total volume of blood, plasma and interstitial fluid were measured. Preliminary data in the 14 cases are sufficiently constant so that the detailed presentation of one typical case will serve as a text adequate to illustrate the general quality and direction of movement of the body fluid pattern observed in the entire group.

[8] Keith, N. M., Rowntree, L. G., and Geraghty, J. T., *Arch. Int. Med.*, 1915, **16**, 547.

[9] Malloy, H. T., and Evelyn, K. A., *J. Biol. Chem.*, 1937, **119**, 481.

[10] Mateer, J. G., Baltz, J. I., Marion, D. F., and MacMillan, J. M., *J. A. M. A.*, 1943, **121**, 723.

[11] Shank, R. E., and Hoagland, C. L., *J. Biol. Chem.*, 1946, **162**, 133.

[12] Archibald, R. M., personal communication.

[13] Wilson, D. W., and Ball, E. G., *J. Biol. Chem.*, 1928, **79**, 221.

[14] Aldersberg, D., and Fox, C. L., *Ann. Int. Med.*, 1943, **19**, 642.

Results. Chart I represents the serial data obtained from a typical case. The patient was a 34-year-old male, seen on the 12th day of his disease. The prehospital period had been marked by malaise, generalized muscular aches and pains, slight anorexia and nausea. There was one mild attack of vomiting 5 days before admission, but the patient had been able to take adequate food and fluids since that episode. Dark urine had appeared 7 days before and visible icterus 3 days prior to hospital admission. Physical examination revealed conspicuous icterus, and an enlarged tender liver. The patient's hospital course was afebrile and with the prompt institution of bed rest and adequate nutrition, convalescence proceeded without unusual event. Measurements of body weight and fluid balance, as well as determinations of blood and plasma volume and interstitial fluid volume were begun the day following admission. It may be noted from the accompanying chart that during the first 2 hospital days there was a fall of 0.8 kg in body weight. This period and the 2 days that followed were marked by the greatest fall in interstitial fluid volume from 237 cc/kg to 223 cc/kg of body weight. The value of 215 cc/kg attained later during convalescence may be taken as a base line. There were slight changes in the same direction but of less magnitude in the blood and plasma volume. Measurements of liver function revealed great impairment as indicated by greatly elevated values for the total bilirubin. the bromsulfalein test and an abnormal thymol turbidity reaction of the serum. It was impressive that despite an adequate fluid intake the urine volume was small compared to the urine output of later convalescence. At this time also the total plasma chloride as well as the urine chloride concentration and total daily urine chloride excretion were low. A water tolerance test done during the first week of admission yielded only 503 cc of urine after the ingestion of 1500 cc of water. By the 17th day of the disease there developed such a marked increase in urine volume that the patient was eliminating between 85 and 90% of his fluid intake. Commensurate with this, greater amounts of chloride appeared in the urine, reaching a peak also on the 17th day, despite the fact that the daily calculated salt intake had been constant (9-10 g) since admission. This same period was further characterized by improvement in liver function. A slight but continued fall in the volume of interstitial fluid, total blood and plasma volumes was noted. On the 21st day of the disease a water tolerance test yielded more than double the previous amount of urine, 1170 cc being obtained. The period from the 21st to the 30th day of disease was characterized by an active diuresis and with this there followed stabilization of the interstitial fluid volume, plasma and blood volumes and a measurable improvement in liver function. Following this period the urine output fell slightly, but plasma chloride values and urine chloride excretion remained at sustained high levels. Little change was noted in the results of the water tolerance tests following the period of diuresis. With the restitution of liver function the initial fall in body weight was overcome and there now appeared a weight gain, despite the fact that the daily caloric intake had been maintained at values between 3000 to 3500 calories since admission. At the time of discharge from the hospital the patient had made a complete recovery, as indicated by maintenance of body weight and restoration of liver function. In addition there had been no significant change in the body fluids, which had been stabilized since the 30th day of the disease. Throughout the period of hospital observation, clinical signs of dehydration were never encountered and no peripheral edema or ascites had been noted.

Discussion. If the convalescent values are used as a base line, it is apparent from the data that a large interstitial fluid compartment exists during the acute phase of infectious hepatitis. In addition there is a tendency to retain or store ingested water, as reflected during this period by the poor urine output of the water tolerance test. That this does not represent inadequate renal function is supported by the fact that numerous routine examinations of the urine for albumin, sugar and formed elements in the sediment were always negative, though no formal renal function tests were performed. In the presence of an increased interstitial fluid compartment, as well as an increased plasma and blood volume, it is difficult to attribute the low urine volume, depressed urine chlorides and tendency to store ingested fluid to simple dehydration.[15] As suspected by Jones and Eaton, this increased interstitial compartment persists until improvement in liver function is manifest. With the mobilization of stored interstitial fluid there is a fall in body weight quite parallel to the amount of fluid lost. A great amount of chloride is apparently withdrawn and resides in this compartment in compliance with the laws of diffusion equilibria. This probably accounts for the low initial plasma chloride and depressed urine chloride excretion. This phenomenon has been previously noted in animals with acute liver injury produced experimentally by means of arsphenamine.[16] When mobilization of the interstitial compartment occurs there is an increase in both urine chloride concentration and total urine chloride excretion. With this adjustment the plasma chloride rises and following the diuresis that may appear at this time, there is less tendency to store ingested water as measured by the water tolerance test. The events of this period are probably set in motion by an improvement in hepatic efficiency. With the establishment of convalescence the body fluid compartments move toward stabilization. There follows a rise in plasma protein values somewhat greater than can be accounted for by the slight fall in plasma volume; this probably reflects improved protein synthesis by the liver. The changes in plasma proteins that may occur independent of alterations in plasma volume have been reported experimentally and are to be found especially where nutritional features are of great importance.[17]

The forces underlying the dynamics of

15 Lyons, R. H., Jacobson, S. D., and Avery, N. L., *Am. Heart J.*, 1944, **27**, 353.

16 Soffer, L. J., Dantes, A. D., and Sobotka, H., *Arch. Int. Med.*, 1937, **60**, 509.

17 Mellors, R. C., Muntwyler, E., Mautz, F. R., and Abbott, W. E., *J. Biol. Chem.*, 1942, **144**, 785.

this changing fluid pattern may be suggested in outline. That there may be endocrine factors at work, such as an antidiuretic substance not effectively inactivated by a poorly functioning liver has been indicated.[4] The role of the pituitary in this mechanism has been suggested,[18,19] and requires further elucidation. Recent data, however, disclose a significant elevation in the level of excretion of biologically active estrogen in the urine during acute infectious hepatitis which attains normal values during late convalescence.[20] It is conceivable that movements in body fluid may follow these alterations in active estrogen and be mediated through a central agency such as the pituitary.

Summary. Interstitial fluid volume (thiocyanate space), total blood volume and plasma volume were measured at frequent intervals in 14 young adult males with acute infectious hepatitis. In each patient, the body fluid movement pattern was similar. Detailed data presented in one typical case disclose an increase in the interstitial fluid compartment during the preconvalescent period and a tendency to store ingested water as measured by a water tolerance test. Diminished plasma and urinary chloride values are also found during this period, probably because of chloride storage in the increased interstitial fluid compartment. With convalescence and the restitution of liver function, the interstitial fluid and its retained chloride are mobilized and the interstitial fluid volume falls to lower values. There is an accompanying fall in body weight and frequently a diuresis follows. Less tendency to store ingested fluid is also observed at this time. Plasma chlorides are now restored and urinary chlorides appear in normal amounts. A slight drop in plasma volume and total blood volume accompany these changes and appear to be independent of alterations in the plasma proteins.

It is suggested that these movements in the body fluids may have an endocrine basis.

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19 Ingram, W. R., Ladd, L., and Benbow, J. T., *Am. J. Physiol.*, 1939, **127**, 544.

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Recovery Curves of Intraventricular Conduction; QRS Aberration.

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Aberrant intraventricular conduction, with change in form and duration of the QRS complex, is commonly encountered in paroxysmal tachycardia of supraventricular origin, and in premature beats from similarly located foci. Such aberration is regarded as being due to fatigue, or to inadequate recovery, of the conducting tissues. The recovery curves of A-V conduction have been carefully studied;[1] similar studies have been made of ventricular muscle strips, but no analogous data are available for the intact mammalian ventricle.

Method. We have used the isolated rabbit heart, perfused through its coronary vessels by a cannula tied into the aorta. The perfusion fluid was prepared according to the formula of Krebs and Henseleit;[2] it was kept at 37°C, and through it was bubbled oxygen containing 5% CO_2. The atria were cut off, and stimulating electrodes were pushed through the upper part of the I-V septum. The electrodes were activated by an electronic stimulator devised, and made for us, by Dr. S. A. Peoples.[3] This device permits variation in the strength of the stimulus, as well as wide

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2 Krebs, H. A., and Henseleit, K., *Z. f. Physiol. Chem.*, 1932, **210**, 33.

3 Peoples, S. A., in press.