THE ANTIDIURETIC ACTIVITY OF THE BLOOD SERUM IN HEALTH AND DISEASE

A Thesis

Presented to

The University of Manitoba

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

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June 1952

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ACKNOWLEDGMENTS

This study was supported by a grant from the National Research Council of Canada to Dr. W. F. Perry. The author wishes to express his appreciation to the staff of the Winnipeg General Hospital for their help and cooperation and to Dr. J. Doupe and to Dr. W. F. Perry for their suggestions and criticisms.

CHAPTER I

INTRODUCTION AND REVIEW OF THE LITERATURE

I. INTRODUCTION

Edema is the term applied to an excessive accumulation of fluids in the tissue spaces and is due to a disturbance of the mechanisms of fluid exchange. Instead of a balance being struck between the inward and outward flow of fluid through the capillary membrane, absorption is exceeded by transudation. The particular factors of the mechanism that are disordered are not always clear, and a satisfactory explanation of all forms of edema cannot be given.

It is generally agreed that the physical factors which regulate water exchange between the tissue spaces and the blood stream are the osmotic and hydrostatic pressures of the fluids in the two situations, the permeability of the capillary membrane, and the patency of the lymph channels. In addition, other mechanisms play a part in the maintenance of the volume and composition of body fluids. Extracellular fluid and its chief electrolyte constituent, sodium chloride, are regulated as far as excretion is concerned by the kidney, and in particular by the terminal segments of the renal tubule. Reabsorption of water that is not obligated to solutes that have escaped reabsorption in the tubules appears to be controlled by the antidiuretic hormone of the posterior lobe of the pituitary. There is evidence to suggest that the reabsorption of sodium chloride is also under hormonal influence, presumably from the adrenal

cortex. The precise disturbances of these mechanisms which lead to edema formation depend upon the type of edema.

II. CARDIAC EDEMA

The retention of water by patients with congestive heart failure is closely associated with the retention of sodium. Burch and associates (4) have demonstrated a delayed turnover and excretion of radioactive sodium in such patients and Gorham et al. (14) have shown that sodium restriction in these patients is of therapeutic advantage. The sequence of events, however, which leads to retention of sodium and water is not beyond dispute. Three main concepts have arisen, one put forward by Starling, a second proposed by Warren and Stead, and a third, which carries Starling's concept a stage further, by Peters.

Starling (32) showed that movement of fluid between the blood capillaries and the adjacent spaces is governed by the balance between the two opposing forces, hydrostatic pressure and colloid osmotic pressure. Transudation is favored by capillary blood pressure and colloid osmotic pressure of perivascular fluid and is opposed by colloid osmotic pressure of plasma and by tissue tension. Fluid can also escape from the extracellular spaces by way of the lymph channels as shown by Drinker (9). According to the Starling concept, failure of the heart causes the blood to back up, increasing the venous pressure and thereby the capillary blood pressure. This provokes transudation of fluid from the capillaries with consequent reduction of the volume of the circulating plasma. This last, in turn, causes the kidneys to reabsorb more than the usual

quantities of sodium and water.

In 1944 Warren and Stead (35) proposed a theory of "forward failure," strongly supported by Starr (33) in 1949, to account for the edema of heart failure, with the following series of events: decrease in cardiac output, decrease in renal blood flow, decrease in glomerular filtration, retention of sodium and then water, increase in blood volume, increase in venous and capillary hydrostatic pressure, transudation into interstitial spaces, edema. This hypothesis was based on the observation in a number of patients of weight gain before venous pressure elevation and on evidence of overexpansion of blood volume as measured by the apparent volume of distribution of Evan's blue dye. It was supported by the report of Merrill (22) of low rates of glomerular filtration and renal plasma flow in patients with congestive heart failure.

A considerable amount of opposition to the "forward failure" theory has been brought forward since it was first published. Landis (17) has pointed out that increased venous pressure with resulting increased capillary hydrostatic pressure is not delayed until gross salt retention has occurred. In addition he has shown that patients with minimal heart failure excrete sodium salts normally. Perera (26) has shown that the formation of edema in congestive heart failure is associated with hemoconcentration. Peters (27) points out that use of Evan's blue dye as a measure of plasma volume is open to question since it can be recovered from lymph and extracellular fluid collections very shortly after injection. He sets forth other physiological evidence to suggest that dehydration and diminished plasma volume are the strongest stimuli to the

kidney to retain sodium and water. Mokotoff et al. (23) showed that the excretion rate of sodium in a cardiac patient with a lowered glomerular filtration rate and on a moderate intake of sodium, may exceed that of a control subject with a normal rate of glomerular filtration who is on a low intake of sodium. There is now a convincing amount of evidence put forward by Newman (25) and others to show that during recompensation of decompensated cardiac patients there may be no significant increase in the glomerular filtration rate. In all these studies the significant change was the increase in the fraction of filtered sodium which was rejected by the tubules in patients during recompensation.

It is hard to escape the conclusion that increased tubular reabsorption is a factor in the decreased excretion of sodium in heart failure. The question which is as yet unanswered in the problem of edema is: what are the stimuli which indicate to the kidney a need for change in rate of excretion of sodium and water, and how are these stimuli misinterpreted in pathological conditions characterized by edema?

Peters (27,28), in an attempt to answer this problem has brought forward another concept of edema which carries the Starling concept a stage further. Peters suggests that the increased capillary hydrostatic pressure in congestive heart failure causes a transudation of fluid from the blood stream. Loss of fluid from the blood stream diminishes the blood volume. This in turn evokes an adrenocortical discharge which promotes reabsorption of salt by the kidneys. The resulting increase of sodium in the serum stimulates antidiuretic activity. This process continues until a new equilibrium is reached in which the loss of fluid

from the blood stream and its return are equal. In support of this concept Peters draws much inferential evidence. He points out the well known fact that adrenocortical hormones prevent wastage of sodium in the urine of patients with Addison's disease. However, there is no direct evidence that the volume of the circulating blood governs the reabsorption of sodium. Verney (34) has shown that the normal stimulus to posterior pituitary antidiuretic activity appears to be the effective osmotic pressure of the serum. They were able to provoke discharge of antidiuretic hormone by injecting hypertonic saline and glucose, but not urea into the carotid arteries of animals. In addition several authors (1,8,31) have reported increased amounts of antidiuretic activity in the urine of patients with congestive heart failure.

Two other factors which may well have some place in the mechanism of cardiac edema are capillary permeability and lymph drainage. Landis (18) has shown that deficient supply of oxygen to the tissues, as may be encountered in congestive heart failure, will cause damage and increased permeability of the capillary membrane. Obstruction to lymph drainage in cases of cardiac edema has been demonstrated by McMaster (21). He found that the lymphatics in congestive heart failure were so dilated and stretched that flow had almost come to a standstill. These factors, while not apparently concerned in the prime mechanism of formation of cardiac edema, undoubtedly play a part.

The validity of the "forward failure" theory of cardiac edema is open to considerable question. There is much evidence to suggest that the venous pressure does rise before fluid and salt retention takes place.

The claim, made by the supporters of this concept, that the glomerular filtration rate is decreased in congestive heart failure is not very well supported. There is a mass of conflicting evidence on this point. At any rate it is doubtful if there is enough drop in glomerular filtration to affect sodium excretion. As pointed out by many investigators the glomerular filtration rate must be decreased by a considerable degree to affect sodium excretion in view of the fact that most of the glomerular filtrate is reabsorbed. The evidence in support of an overexpansion of blood volume is based upon the apparent volume of distribution of Evan's blue dye. It is likely, as pointed out by Peters, that Evan's blue dye measures more than just blood volume. Blood volume studies in cardiac failure with edema estimated by more reliable means are in favor of hemoconcentration. In view of the conflicting evidence put forward in support of the "forward failure" concept of cardiac edema it is doubtful if much weight can be placed on this theory until the evidence is clarified.

There is little that can be brought forward in opposition to the Starling concept of the mechanism of edema formation in congestive heart failure. However, the sequence of events suggested by Peters, while very logical, is not by any means proven. The problem that faces the supporters of this theory is the nature of the renal response in cardiac edema. It is agreed that in congestive heart failure the kidney excretes less sodium and water but the stimulus which indicates to the kidney a need for change in the rate of excretion is unknown. It is probable that there is hemo-concentration in congestive heart failure but the suggestion made by

Peters that a reduced blood volume causes the kidney to retain salt is not as well substantiated. The suggestion has been made that the adrenal cortex secretes a hormone which acts upon renal tubules to increase the absorption of salt. However, such a hormone has not been demonstrated, with the exception of desoxycorticosterone which does not occur naturally in the adrenal cortex.

At the present time there is not a well supported theory of the method by which renal salt and water retention is obtained. Much of the literature of the mechanism of cardiac edema deals with the investigation of this problem. Many of the processes which play a part in the development of edema have been elucidated but there is not agreement between investigators as to the sequence of events.

III. EDEMA OF PORTAL OBSTRUCTION

In advanced cirrhosis of the liver and other conditions which cause widespread destruction of the liver and replacement by scar tissue, ascites is prone to develop, and later edema of the lower extremities. These have been generally attributed to obstruction of the portal venous system. However, it is well known that ascites may not develop, even in patients with far advanced cirrhosis, despite very high portal venous pressures. Starling (32) first demonstrated that certain parts of the circulation, especially the liver and portal circulation, appear to be more permeable to protein. In these areas there has been demonstrated a continuous circulation of protein from blood stream to extracellular fluid and back through the lymphatic

vessels to the blood stream. This may in part explain the stubborn response to therapy of the ascitic accumulation in these conditions.

Butt et al. (6) have demonstrated that ascites and edema make their appearance when serum albumin falls. Weech and his associates (36) have shown that as the serum albumin falls the volume of the circulating plasma diminishes because the decrease of the colloid osmotic pressure of the plasma promotes transudation from the blood capillaries. Peters (27,28) has suggested that this decrease in circulating plasma volume invokes the renal regulatory mechanisms as in cardiac edema. He cites as evidence, the fact that increased antidiuretic activity has been found in patients with cirrhosis (8,30). This suggestion is obviously open to the same criticism as previously cited in relation to the edema of congestive heart failure. It is not always possible to demonstrate a fall in serum albumin in cases of cirrhosis with edema, and several authors (24) have found that as the serum albumin falls the circulating plasma volume remains the same or increases. In spite of the work which pointed to a correlation between the fall in the concentration of serum albumin and the formation of edema, the only conclusion possible at the present time is that a low level of serum albumin, or of total protein, is not the deciding factor in the overproduction of tissue fluid.

IV. RENAL EDEMA

The edema of acute glomerulonephritis differs in distribution from most generalized edemas in certain respects. It is less subject to gravity and may appear suddenly in the hand or face without any relation to dependency. It is associated with other evidences of vasomotor instability and urticarial reactions are not uncommon. The edema fluid has been shown to contain more protein than does the edema fluid in other non inflammatory transudative processes (29). All these phenomena suggest the existence of a diffuse vascular disorder which involves derangement of vasomotor control. This, together with the not uncommon association of heart involvement in acute nephritis would seem to be the mechanism of production of edema.

In the nephrotic syndrome vasomotor disturbances and heart failure may continue to play a part in the production of edema but reduction of the protein osmotic pressure appears to be the most important factor. Farr and Van Slyke (12) have produced evidence to suggest a correlation between the hypoproteinemia and the development of edema. Luetscher and Hall (20) have observed that protein deficiency in nephrosis was associated with lowered rates of glomerular filtration and sodium excretion. This evidence has been questioned by Burnett et al. (5) who could demonstrate no such correlation. In addition, antidiuretic activity has been reported in the urine of patients with nephrosis (31). These findings are of course open to the criticisms which have been levelled at similar evidence in previous sections.

V. ANTIDIURETIC HORMONE OF THE POSTERIOR LOBE OF THE PITUITARY

Throughout the literature concerning the mechanism of edema formation in various conditions there has been the mention of the antidiuretic principle of the posterior lobe of the pituitary. Robinson and Farr (31) investigating certain edema states of non-cardiac origin found increased amounts of an antidiuretic substance in the urine, while Bercu et al. and others (1,8) recently reported similar findings in subjects with congestive heart failure.

Eversole, Birnie and Gaunt (10,11) have shown that in rats the liver inactivates pitressin; from this observation one might expect that patients with liver damage would have increased amounts of antidiuretic substances in the body, and in fact, Ralli et al. (30) found that cirrhotic patients with ascites excreted more than normal amounts of an antidiuretic substance. Hall, Frame and Drill (15) have also reported the urine of cirrhotic patients to contain a substance with antidiuretic activity but were unable to demonstrate such activity in the urine of normal subjects. Recently Dochios and Dreifus (8) have shown an increased antidiuretic activity in the urine of patients with cirrhosis.

Accordingly, because of the confusion regarding the mechanism of edema formation and the possibility that it might be related to the antidiuretic substance of the posterior lobe of the pituitary, it appeared to be of interest to determine the levels of antidiuretic activity in the serum of patients with cardiac edema and in the serum

of patients with liver disease, using the method devised by Birnie et al. (2,3).

CHAPTER II

THE EXPERIMENTAL METHOD

The assay of serum antidiuretic substance was made on venous blood. The serum was separated from the cells as rapidly as possible by centrifugation and used for assay within one hour of being drawn. This time limit was imposed because in agreement with Birnie (2) the activity was found to be markedly diminished after 24 hours storage. The assay was performed on male rats weighing approximately 200 gm. The Heller and Urban procedure, as modified by Birnie et al. (2,3), was used. The rats were isolated in a quiet room, fasted but allowed water ad lib for 18 hours before being used. Test groups of three rats were placed in metabolism cages.[1] Five per cent of the body weight of tap water, warmed to body temperature was administered to the animals by gavage. This dose was repeated one hour later and one hour after this second dose the urine from each group was measured, then discarded. A third similar dose of water was then administered and the test material injected intraperitoneally. The dose was 0.5 ml. serum per 100 gm. of rat, collected not more than one hour before or 0.5 ml. physiological saline per 100 gm. of rat. Following this the urine output of each group was measured after three hours and in many cases the chloride content determined by the Volhard Harvey method (16).

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[1] Because of the slight variation in the weight of individual rats, groups of three were used. In this way the weight of each cage of animals was more closely approximated and the water diuresis which was induced was also comparable.

The water excreted during the three hours was expressed as its percentage of the "water load," i.e. the total amount of water given, minus that amount excreted prior to injection of the test material. The animals were not used at intervals of less than seven days and those which received serum were not used more than twice, because of the possibility of protein sensitization.

In the various control saline-injected groups it was found that the percentage of the "water load" which was excreted by the end of the experimental period varied from 64 per cent to 79 per cent with a mean of 72.6 per cent. In all but a few cases the experimental serum-injected groups excreted less water than did their controls. Anti-diuretic activity was expressed in units (A. D. units); these were calculated by subtracting the per cent of the "water load" excreted by the serum-injected rats from the per cent of the "water load" excreted by the control saline-injected rats, run simultaneously.[2]

Healthy adult people employed in the Winnipeg General Hospital were used as normal subjects. There were no special precautions taken with regard to food and fluid intake. The patients with disease were drawn from the public wards of the Winnipeg General Hospital. Estimations were carried out on the patients with congestive heart failure as soon after admission as possible. Therapy, other than bed rest, was withheld until the blood was drawn. As far as could be

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[2] This method of expressing antidiuretic activity was first suggested by Lloyd and Lobotsky (19) and has been used in this work in order to facilitate comparison of results with those of other workers.

controlled conditions of temperature and humidity. The sex of the beetles was determined by the method described by Park (10). The only reliable external sexual characteristic for any stage is found in the pupal stage. The pupae were placed, ventral surface up, on the stage of a binocular microscope and examined under low power. On the ventral surface of the posterior terminal segment, the female has a pair of small appendages appearing very much like miniature mammary glands. These appendages are reduced to indistinct elevations in the male. The insects used in this study were separated into males and females on the basis of this characteristic anatomical difference. The pupae of each sex were reared separately in large pyrex baking dishes containing a standard food medium made up of 95% whole wheat flour sifted twice through a number 60 wire mesh screen and 5 per cent finely powdered brewer's yeast by weight (9). The yeast was thoroughly mixed through the flour so that all parts of the mixture were the same from the standpoint of nutritional value. Only the sifted flour was used in making up the food medium. The purpose in separating the bran from the flour and using only the sifted portion was to facilitate the separation of eggs and first instar larvae from the flour. It is obvious that the presence of bran would make the task of separating the eggs or tiny larvae virtually impossible.

Experimental conditions of temperature, humidity and age of insects were controlled as closely as possible. The temperature and relative humidity were maintained at 28.5 degrees C. and 70 - 75 per cent respectively (9) (10). Temperature has a marked effect upon the number of eggs

ascertained the patients were actively retaining fluid at the time of estimation and diuresis had not begun. The cases of liver disease were selected from those patients with liver disease in its ascendency. Patients believed to be in a recovery phase were not used. There were no restrictions imposed on any of the groups and food and fluid were allowed ad lib. All estimations of antidiuretic activity were carried out in the early afternoon. Serum was drawn shortly after the noon meal and used within one hour.

glass jars containing equal volumes of the standard food material. Each test lot was placed in a numbered jar. The treated insects were kept in the jars for a certain period of time during which mortality of some of the exposed insects was induced. This period of time was 8 days for Experiment A and 7 days for Experiments B and C. It was previously noted that after the sixth day any further mortality was negligible; this being the case, it was felt that 7 days was sufficient for insects to succumb to lethal doses of D.D.T. The sex of beetles which died during the course of the experiment was determined by gently squeezing the abdomen of the dead insect and examining the extruded genitalia. Knowledge of the exact number of males and females dead at any given time was essential for the calculation of rate of oviposition.

After the exposed insects had been allowed to remain in the glass jars for the required 7 or 8 days, the male and female survivors were paired according to the design indicated in Table I. For example, the survivors of replicate lot 1 (males) were paired with an equal number of survivors from replicate lot 5 (females) or vice versa, according to which sex suffered the greatest mortality. The paired lots were placed in the wide-mouthed glass jars each containing an equal volume of the standard food medium. It is obvious that the number of pairs is governed by the replicate lot showing the higher mortality. The replicate groups combined as follows: 1 and 5, 2 and 6, 3 and 7, 4 and 8, 9 and 13, etc. This uniform method of pairing was adopted in each of the four experiments. Since each combination of sexes and treatments

CHAPTER III

THE RESULTS

The variability of the assay procedure is shown in Table I by the values obtained on the three separate groups of animals injected simultaneously with serum from one subject. These three groups excreted 36.8 per cent, 33.8 per cent and 37.7 per cent of the "water load," giving antidiuretic values for this particular serum of +35.6, +38.6, and +34.7 A. D. units. Similar results were obtained using the serum from a normal subject with very little antidiuretic activity. Fig. 1 shows serum levels of antidiuretic activity in different degrees of tissue hydration. Two normal males ingested 6.5 litres of tap water over a four-hour period. At the end of this time their sera were found to be slightly diuretic; the antidiuretic activity being -2 A. D. units in both cases. One week later the same two subjects withheld all fluids for thirty hours, solid food only being consumed during this time. The antidiuretic activity of the serum at the end of this period was found to be +12 and +23 A. D. units. A somewhat similar difference was found between the serum of a rat allowed to drink ad lib and that of a rat in which water was withheld for eighteen hours.

In Table II are shown the results of thirteen determinations of antidiuretic activity in the serum of thirteen normal subjects. Cases two, six, and eight were examined twice on different occasions. The activity ranged from -7 to +34.5 A. D. units with an average of +16.6 A. D. units. In Table III are shown the results of 12 separate

TABLE I

THE VARIABILITY OF THE ASSAY PROCEDURE

Assays	Per Cent "Water Load" Excreted			Antidiuretic Activity (A.D. Units)		
	Cage 1	Cage 2	Cage 3	Cage 1	Cage 2	Cage 3
Serum I (Normal)	73.1	72.7	71.8	±2.4	±2.8	±3.7
Control	75.5					
Serum II (Heart Failure)	36.8	33.8	37.7	±35.6	±38.6	±34.7
Control	72.4					

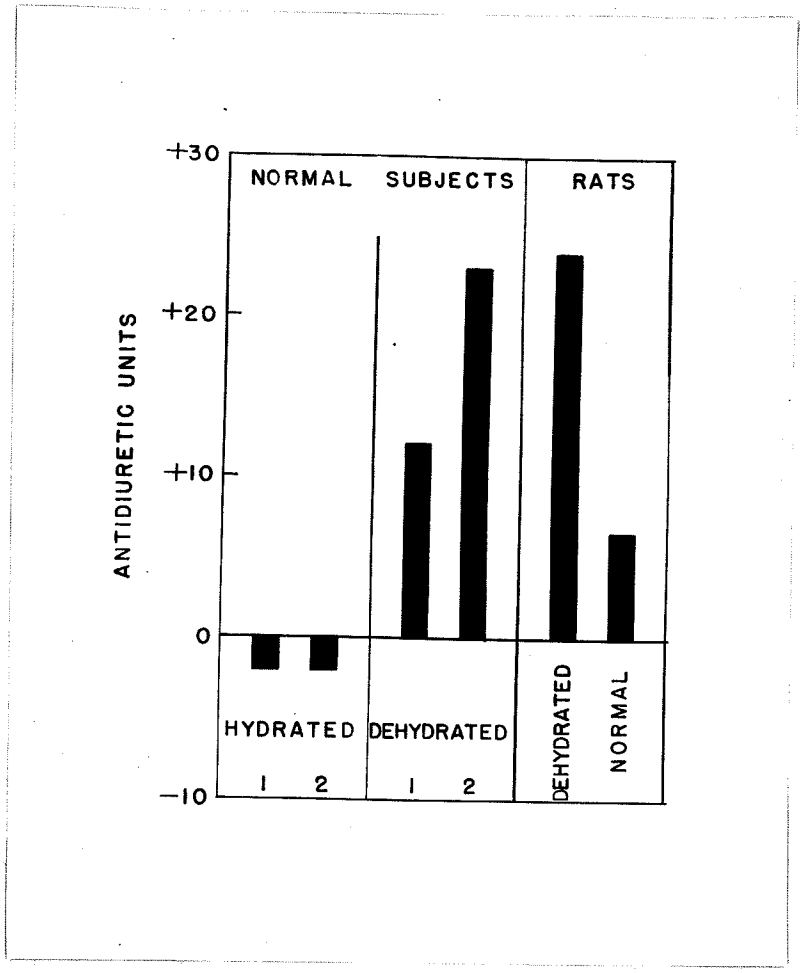

Figure 1

The effect of hydration on the serum antidiuretic activity.

TABLE II

SERUM ANTIDIURETIC ACTIVITY OF NORMAL SUBJECTS

Case No.	Age	Sex	Antidiuretic Activity (A.D. Units)
1	56	M	+12.5
2	22	M	+16
	22	M	+ 1.5
3	32	M	+ 0.5
4	35	M	- 7
5	26	F	+30.1
6	28	F	+27.1
	28	F	+23.5
7	23	M	+19.5
8	24	M	+34.5
	24	M	+33.5
9	22	F	+32.5
10	26	F	+ 9.5
11	24	M	+21
12	21	F	+ 2
13	27	F	+ 9.5

Mean +16.6 A.D. Units

TABLE III

DETAILS OF SUBJECTS WITH CONGESTIVE HEART FAILURE

Case No.	Diagnosis	Age	Sex	Clinical Summary	Antidiuretic Activity (A.D. Units)
1	Rheumatic Heart Disease	49	F	Pitting edema + + + Ascites + +	+33 + 5.5
2	Hypertensive Cardiovascular Disease	77	M	Pitting edema + + Ascites + +	+28.5 +24.5
3	Hypertensive Cardiovascular Disease	69	F	Pitting edema + + + Ascites + + + Pleural effusion + +	+27
4	Hypertensive Cardiovascular Disease	51	F	Pitting edema + + Ascites + +	+37
5	Cor Pulmonale	68	M	Pitting edema + + + + Ascites + + + Pleural effusion + + +	+42.1
6	Hypertensive Cardiovascular Disease	77	M	Pitting edema + + + Ascites + + Pleural effusion + +	+39.5
7	Arteriosclerotic Cardiovascular Disease	77	M	Pitting edema + + + Ascites + + Pleural effusion + +	+ 2.5
8	Hypertensive Cardiovascular Disease	48	F	Pitting edema + + + Ascites + + + Pleural effusion + +	+24.5
9	Cor Pulmonale	58	M	Pitting edema + + + + Ascites + +	+ 2.5
10	Arteriosclerotic Cardiovascular Disease	69	F	Pitting edema + + + Ascites + + Pleural effusion + +	+12

Mean +23.2 A.D. Units

estimations on 10 subjects with congestive heart failure. All these patients had gross pitting edema and ascites; all but four had pleural effusions[1]. They were admitted to hospital because of symptoms associated with increasing water retention. The sera were tested before treatment was instituted and as soon as possible after admission. The range of antidiuretic activity was from +2.5 to +42.1 A. D. units with an average of +23.2 A. D. units, higher than the mean results for normal subjects. However, when the results of the two groups were compared by an analysis of variance it was found that the difference was not significant ($P > 0.05$). The level of antidiuretic activity in the group of patients did not correspond to the extent of edema; data for fluid intake was not available for correlation.

Table IV shows the extent of liver damage in a group of nine patients with liver disease. All cases had a raised serum bilirubin and abnormal cephalin flocculation tests; all but one had abnormal thymol turbidity tests. Twelve separate estimations for antidiuretic activity on the nine patients were done. The range of antidiuretic activity was from +4.5 to +37 A. D. units with an average of +20.9 A. D. units. An analysis of variance showed that there was no significant difference between this group and the normal group ($P > 0.05$). The antidiuretic activity of the individuals' sera could not be correlated with the extent of liver damage.

The sera from three cases of Addison's disease and single cases

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[1] Details of the case histories of these subjects and those following can be found in the Appendix.

TABLE IV

DETAILS OF SUBJECTS WITH LIVER DISEASE

Case No.	Diagnosis	Age	Sex	Clinical Summary	Antidiuretic Activity (A.D. Units)
1	Portal Cirrhosis	63	F	Gross ascites and edema Serum bilirubin 4.5 mgms.% Ceph. Floc.+++ Thymol Turb. 0.04	+22.5 + 7.5
2	Infectious Hepatitis	24	M	Serum bilirubin 11.9 mgms.% Ceph. Floc.++++Thymol Turb. 0.04	+36.5 +25.1
3	Obstructive Jaundice	74	M	Serum bilirubin 19.2 mgms.% Ceph. Floc.+++ Thymol Turb. 0.05	+35.1
4	Homologous Serum Jaundice	40	F	Serum bilirubin 4.5 mgms.% Ceph. Floc.++++Thymol Turb. 0.09 Prothrombin Time 48%	+ 5.1
5	Leukemic Infiltration of the Liver	72	F	Serum bilirubin 16.0 mgms.% Ceph. Floc.++++ Thymol Turb. 0.3	+ 4.5
6	Obstructive Jaundice	69	M	Serum bilirubin 13.5 mgms.% Ceph. Floc.+++ Thymol Turb. 0.04	+26.1
7	Portal Cirrhosis & Obstructive Jaundice	80	M	Serum bilirubin 14.3 mgms.% Ceph. Floc. ++ Thymol Turb. 0.01	+ 7.0 +37.0
8	Infectious Hepatitis	28	M	Serum bilirubin 8.2 mgms.% Ceph. Floc.+++ Thymol Turb. 0.07	+14.5
9	Portal Cirrhosis	67	M	Serum bilirubin 2.5 mgms.% Ceph. Floc.+++ Thymol Turb. 0.08	+30.0

Mean +20.9 A.D. Units

of nephrotic syndrome, lymphatic edema, Hodgkin's disease, and lymphatic leukemia were tested. As shown in Table V the values fell within the normal range.

The chloruretic activity of the sera was estimated by comparing the amount of chloride excreted in the three hours after the injection of the test material with the amount excreted by the animals injected with saline. As shown in Table VI human sera had no effect on chloride excretion despite an effect on water excretion. It thus differed from pitressin which was chloruretic as well as antidiuretic.

TABLE V

SERUM ANTIDIURETIC ACTIVITY
OF MISCELLANEOUS SUBJECTS

Case No.	Diagnosis	Age	Sex	Antidiuretic Activity (A.D. Units)
1	Addison's Disease	54	F	+18.5
2	Addison's Disease	21	M	+20.0
3	Addison's Disease	32	M	+14.5
4	Nephrotic Syndrome	62	M	+21.0
5	Lymphatic Edema	60	M	+16.5
6	Hodgkin's Disease	20	M	+37.6
7	Lymphatic Leukemia	50	M	- 3.5

TABLE VI

COMPARISON OF CHLORURETIC AND ANTIDIURETIC ACTIVITY

Substance	Chloride Excretion Mgms. in 180 Minutes			Antidiuretic Activity (A.D. Units)		
	Number of Estimations	Average	Range	Number of Estimations	Average	Range
Saline	11	12.8	6.5 - 20.4	11	0	-
Pitressin 5 mu.	9	46.5	28.0 - 67.0	9	12.6	2.0 - 29.6
Pitressin 10 mu.	8	60.8	29.7 - 91.0	8	18.3	10.0 - 27.5
Pitressin 20 mu.	9	76.5	34.0 -113.0	10	31.6	22.5 - 48.0
Sera - Normals	12	11.4	5.4 - 22.2	16	16.6	-7.0 - 34.5
Sera - Congestive Heart Failure	11	8.9	0.0 - 22.2	12	23.2	2.5 - 42.1
Sera - Liver Disease	9	10.9	3.0 - 31.7	12	20.9	4.5 - 37.0
Sera - Miscellaneous	5	8.4	3.0 - 13.8	7	17.4	-3.5 - 35.0

CHAPTER IV

DISCUSSION OF THE RESULTS

Birnie et al. (2,3) found that rat serum contains a substance with both antidiuretic and chloruretic activity which is related to the degree of hydration of the animal and for these reasons is believed by them to originate in the neurohypophysis. Dicker and Ginsberg (7) have also recently shown that the serum of rats contains an antidiuretic substance but they further found that it was not present in plasma. It is not apparent from their data whether the serum activity is related to hydration or not. They suggest that the active substance is a product of blood coagulation. More recently Gaunt (13) has been unable to confirm the work of Dicker and Ginsberg, finding plasma and serum to be equally antidiuretic. Also the results of Birnie et al. (2,3) and those reported here for the human indicate the amount of this substance can alter with the degree of hydration of the body and for this reason it would seem unlikely that it is an artefact. In addition several investigators (1,8,15,30,31) have reported the presence of a substance with similar activity in the urine.

The antidiuretic substance in human serum differs from that in rat serum and also from pitressin in being not chloruretic. Whether or not the activity measured in human serum is derived from the neurohypophysis and whether it is identical with antidiuretic substance excreted in urine remains to be established. Although the activity in serum from two healthy persons has been shown to alter with variations

in the degree of tissue hydration, from the rather wide variations in the values obtained on normal persons taking fluids as desired, it would seem not improbable that the antidiuretic activity measured is a net effect of antidiuretic and diuretic substances in the serum, as suggested by Lloyd and Lobotsky (19). As shown, the variation is too great to be ascribed to inconsistencies in the assay method.

In any case, alterations in the level of activity do not seem to be responsible for the retention of water associated with congestive heart failure, nor has the degree of liver impairment been shown to affect the level of activity in the serum. This is in contrast to the finding of Dochios and Dreifus (8), who reported increased amounts of antidiuretic substance, which correlated with the degree of clinical edema, in the urine of such patients. This suggests that serum antidiuretic substance as well as differing from pitressin in not being chloruretic is also not identical with urine antidiuretic substance.

CHAPTER V

SUMMARY AND CONCLUSION

It has been demonstrated that human serum contains a labile substance which exerts an antidiuretic effect when injected into hydrated rats and which could vary with the extent of hydration. The antidiuretic activity of the sera of a group of 10 patients with congestive heart failure was compared with that of a normal group. No significant difference in antidiuretic activity was demonstrated. Nine subjects with liver disease also showed values within the normal range.

It was concluded that the alterations in the serum level of antidiuretic activity were not responsible for the water retention associated with congestive heart failure and liver disease. The sera of all cases studied were shown to be non-chloruretic, thus differing from the antidiuretic principle present in posterior pituitary extracts.

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APPENDIX

CASE HISTORIES FOR SUBJECTS WITH CONGESTIVE HEART FAILURE

1. Mrs. K. M., Winnipeg General Hospital No. 12005. A 49 year old female patient with symptoms of congestive heart failure since 1946 who has required continuous therapy in the Outpatient Department of the Winnipeg General Hospital. She gave a history of rheumatic fever in childhood and there was a loud mid-diastolic murmur at the apex of the heart. The blood pressure was 120/75 and the urine was normal. She had been diagnosed as a case of mitral stenosis with congestive heart failure. The patient was admitted to hospital March 28, 1950 complaining of increasing dyspnoea and progressive swelling of the legs for some weeks. The jugular venous pressure was markedly elevated. There was considerable pitting edema of the legs and sacral area and moderate ascites. The heart murmur was unchanged and the patient was fibrillating. A serum antidiuretic level was estimated on April 3, 1950 at which time the patient's weight was 128 lbs. After therapy was instituted the weight fell to 111 lbs. and the edema cleared. She was readmitted on May 22, 1950 with the same symptoms and signs. A serum antidiuretic level was done on May 23, 1950 at which time her weight was 125 lbs. Following therapy her weight fell to 113 lbs.

2. Mr. W. H., Winnipeg General Hospital No. 32658. A 77 year old white male admitted on April 13, 1950 with symptoms of progressive dyspnoea for the past six weeks. Examination revealed moderate dyspnoea with some cyanosis. The jugular venous pressure was increased, the heart was enlarged and regular, the blood pressure was 215/110.

The liver was enlarged and ascites was present. Moderate pitting edema of the legs was noted. The electrocardiogram showed myocardial damage and a left bundle branch block. Renal function was normal. An estimation of serum antidiuretic activity was performed on April 18, 1950 at which time the patient was gaining weight. This was repeated on May 23, 1950 when the patient was readmitted, again in congestive heart failure. His weight fell on therapy from 163 lbs. to 152 lbs. He was considered to be a case of hypertensive cardiovascular disease with congestive heart failure.

3. Mrs. E. G., Winnipeg General Hospital No. 33348. A 69 year old white female admitted on May 2, 1950 with symptoms of dyspnoea and edema for several months. She was known to be suffering from diabetes mellitus and hypertension and had been followed in the Winnipeg General Hospital for some years. On admission she was very dyspnoeic and somewhat cyanozed. The jugular venous pressure was increased and there was pitting edema to the shoulders. There was a left pleural effusion, the heart was enlarged and regular, the blood pressure was 210/130. Marked ascites was present. The electrocardiogram showed myocardial damage and a left bundle branch block. Renal and liver function tests were normal and the blood sugar was 150 mgms. per cent. A serum antidiuretic estimation was carried out on May 5, 1950. The patient continued to be very ill and died on May 11, 1950. She was considered to be a case of hypertensive cardiovascular disease with congestive heart failure and diabetes mellitus.

4. Mrs. H. C., Winnipeg General Hospital No. 32816. A 51 year old white female patient admitted on April 18, 1950 with symptoms of progressive dyspnoea for six months. She was a very frail little woman with obvious dyspnoea and some cyanosis. The jugular venous pressure was markedly elevated and there was considerable enlargement of the heart. The heart action was regular, there were no murmurs and the blood pressure was 210/140. The liver was palpable and there was moderate ascites. Peripheral edema was present to the knees. The electrocardiogram showed left ventricular strain, the kidney function was normal. A serum antidiuretic level was done on May 5, 1950 at which time the patient's weight was 93 lbs., unchanged from admission. Further therapy with mercurial diuretics reduced the patient's weight to 83 lbs. She was considered to be a case of hypertensive cardio-vascular disease with congestive failure.

5. Mr. S. C., Winnipeg General Hospital No. 4131. A 68 year old white male patient admitted with symptoms of increasing dyspnoea and edema for several weeks. He had previously been diagnozed as a case of severe emphysema with bronchiectasis and gave a history of chronic cough and expectoration for thirty years. When admitted on May 17, 1950 he was extremely dyspnoeic and cyanozed. There was marked clubbing of the fingers and toes and the jugular venous pressure was elevated. There were bilateral large pleural effusions and early pulmonary edema was noted. His blood pressure was 130/80 and no murmurs were heard; the heart was regular. Marked ascites was present

and the patient was grossly edematous to the upper chest. He was diagnozed as a case of cor pulmonale with severe congestive heart failure. A serum antidiuretic level was estimated on May 18, 1950. The patient was too ill to be weighed and on May 19, 1950 the patient died.

6. Mr. F. P., Winnipeg General Hospital No. 34255. A 77 year old white male patient admitted June 2, 1950 in an acute attack of pulmonary edema. He gave a history of increasing shortness of breath for some weeks with onset of peripheral edema in the last two weeks. On examination he was dyspnoeic and cyanotic. The jugular venous pressure was elevated and there were many crepitations and early pleural effusions in the lung fields. The heart was enlarged and fibrillating and the blood pressure was consistently 190/100; there were no murmurs. The liver was palpable and there was some ascites. Moderate peripheral edema was noted. The electrocardiogram revealed left ventricular strain. Liver and renal function tests were normal. On June 6, 1950 a serum antidiuretic level was done before any therapy other than bed rest was instituted. The weight fell from 120 lbs. to 105 lbs. on treatment. He was diagnozed as a case of hypertensive cardiovascular disease with congestive heart failure.

7. Mr. W. H., Winnipeg General Hospital No. 34438. A 77 year old white male admitted June 9, 1950 with symptoms of dyspnoea and increasing edema for the past month. He had been treated for congestive heart failure in the Winnipeg General Hospital some years previously. On

physical examination he was not cyanotic, the jugular venous pressure was elevated and there was a left pleural effusion. The heart was regular and enlarged to the left, the blood pressure was 125/80. The liver was slightly enlarged and there was a moderate degree of ascites. Pitting edema was present to the thighs. The electrocardiogram showed evidence of myocardial damage. Liver and renal function tests were normal. A serum antidiuretic level was done on June 9, 1950. The patient lost 32 lbs. in weight on therapy and was considered to be a case of arteriosclerotic cardiovascular disease with congestive heart failure.

8. Mrs. A. G., Winnipeg General Hospital No. 2770. A 48 year old white female patient followed in this hospital since 1946. She first complained of dyspnoea and swelling of the ankles at that time and was found to have severe hypertension with congestive heart failure. Since then she has required continuous medical care and frequent hospital admissions. She had developed hypertensive changes in her retinae, kidneys and brain in the interval. She was admitted in severe pulmonary edema on June 12, 1950. The jugular venous pressure was markedly elevated, there was gross pulmonary edema and early pleural effusions were present bilaterally. The blood pressure was 220/150, the heart was enlarged but regular. There was moderate ascites and gross edema of the legs to the thighs. A serum antidiuretic level was estimated on June 21, 1950 at which time the patient was grossly edematous and the weight was 160 lbs. Following therapy the patient's weight fell to 147 lbs.

9. Mr. T. W., Winnipeg General Hospital No. 34904. A 58 year old Chinese male patient admitted on June 26, 1950 with symptoms of increasing dyspnoea and edema formation for one month. On examination the patient was very short of breath and markedly cyanozed. His jugular venous pressure was elevated, and the chest was fixed and barrel shaped. The heart was enlarged and regular; there were no murmurs and the blood pressure was 110/60. The liver was palpable and tender and there was marked ascites and edema to the sacral area. The radiological appearance of the chest was consistent with pulmonary emphysema and fibrosis, the electrocardiogram demonstrated a right ventricular preponderance. Hepatic and renal function were normal. Serum antidiuretic activity was measured on June 27, 1950 at which time the patient weighed 137 lbs. After therapy was instituted the patient lost 24 lbs. He was diagnozed as a case of cor pulmonale with congestive heart failure.

10. Mrs. A. D., Winnipeg General Hospital No. 32776. A 69 year old white female patient admitted April 17, 1950 with symptoms of increasing dyspnoea and edema for six weeks. On examination she was quite short of breath and somewhat cyanozed. The jugular venous pressure was elevated and there was a small right pleural effusion. The heart was enlarged and fibrillating. There were no murmurs; the blood pressure was 150/90. The liver was palpable and there was moderate ascites. Peripheral edema to the knees was noted. The electrocardiogram revealed myocardial damage and the renal function was intact. A serum

antidiuretic level was measured on April 18, 1950. On therapy the patient's weight fell from 136 lbs. to 122 lbs. She was diagnozed as a case of arteriosclerotic cardiovascular disease with congestive heart failure.

CASE HISTORIES FOR SUBJECTS WITH LIVER DISEASE

1. Mrs. A. O., Winnipeg General Hospital No. 16239. A 63 year old female patient admitted February 26, 1950 with complaints of jaundice and increasing edema. She had been suffering from these complaints since 1947 and had been under continuous medical care since that time. On examination she was an obese, yellowish, elderly woman with many naevi over her body. The jugular venous pressure and blood pressure were normal. The liver was large and firm and the tip of the spleen was palpable. There was a very marked ascitic accumulation which had been evacuated many times previously. There was considerable edema of the legs. On March 28, 1950 a serum bilirubin was 4.5 mgms. per cent, cephalin flocculation +++, thymol turbidity 0.04, serum proteins 2.8/4.3. A serum antidiuretic level was estimated on March 28, and on March 29, 1950. Her general condition remained unchanged and she died of cirrhosis of the liver some weeks later.

2. Mr. H. J., Winnipeg General Hospital No. 32288. A 24 year old white male admitted April 3, 1950 with symptoms of jaundice, weakness, and loss of appetite for five weeks. On examination he was markedly jaundiced and had obviously lost a considerable amount of weight. The

liver and spleen were palpable but otherwise there were no physical abnormalities detectable. Serum antidiuretic estimations were carried out on April 6, and on April 10, 1950. At this time the serum bilirubin was 11.9 mgms. per cent, the alkaline phosphatase was 21 King units, the cephalin flocculation was ++++, the thymol turbidity was 0.04, the prothrombin time was normal. The patient was diagnozed as a case of infectious hepatitis and subsequently made a complete recovery.

3. Mr. P. O., Winnipeg General Hospital No. 31849. A 74 year old white male admitted March 22, 1950 with symptoms of abdominal pain and increasing jaundice for one month. On physical examination he was markedly icteric and almost totally anorexic. There was a large mass in the right upper quadrant associated with some liver enlargement but physical examination was otherwise completely normal. There was bile in the urine and no urobilinogen. The serum bilirubin was elevated as was the serum alkaline phosphatase. A serum antidiuretic estimation was done on April 10, 1950. At this time the serum bilirubin was 19.2 mgms. per cent, the serum alkaline phosphatase was 138 King units, the cephalin flocculation was +++, the thymol turbidity was 0.05 and the prothrombin time was 60 per cent of normal. An exploratory operation was done on April 12, 1950 and a carcinoma of the gall bladder with complete common bile duct obstruction was found. The patient died on April 16, 1950 and a post mortem confirmed the diagnosis.

4. Miss E. L., Winnipeg General Hospital No. 27621. A 40 year old white female admitted February 25, 1950 for surgical treatment of a

congenital malformation of the left arm. She had been admitted for operative therapy on several occasions; the last occasion being three months previously, at which time several blood transfusions were given. On March 29, 1950 she developed a homologous serum jaundice and became quite icteric. The liver was palpable but the spleen was not. A serum antidiuretic level was estimated on April 10, 1950. At this time there was bile and an excess of urobilinogen in the urine, the serum bilirubin was 4.5 mgms. per cent, the alkaline phosphatase was 23.8 King units, the cephalin flocculation was ++++, the thymol turbidity was 0.09, and the prothrombin time was 48 per cent of normal. The patient subsequently made an uneventful recovery from the hepatitis.

5. Mrs. T. P., Winnipeg General Hospital No. 32561. A 72 year old white female admitted on April 11, 1950 with symptoms of jaundice, weakness, and anorexia for six weeks. On examination the patient was icteric and somewhat wasted. There was a generalized lymphadenopathy of small, discrete, soft nodes. The liver and spleen were both palpable but otherwise physical examination was negative. Examination of the blood and bone marrow revealed that the patient was suffering from myelogenous leukemia; the white blood count was 41,000. There was bile and an excess of urobilinogen in the urine. The serum bilirubin was 16 mgms. per cent, the alkaline phosphatase was 17 King units, the cephalin flocculation was ++++, the thymol turbidity was 0.3, and the prothrombin time was normal. A serum antidiuretic level was estimated on April 14, 1950. The patient continued to go downhill

and died on April 25, 1950. A post mortem confirmed the diagnosis of myelogenous leukemia and the liver was found to be diffusely infiltrated with leukemic cells.

6. Mr. L. A., Winnipeg General Hospital No. 33437. A 69 year old white male admitted May 5, 1950 with symptoms of jaundice, anorexia, and loss of weight for the previous four weeks. On examination he was quite icteric and had obviously lost some weight. The only abnormal physical finding was a large mass in the right upper quadrant which was hard and irregular. There was bile in the urine but no urobilinogen, the serum bilirubin was 13.5 mgms. per cent, the alkaline phosphatase was 30 King units, the cephalin flocculation was +++, and the thymol turbidity 0.04, the prothrombin time was normal and the serum proteins were 3.3/1.6. A serum antidiuretic estimation was done on May 18, 1950. An exploratory laparotomy was performed on May 22, 1950 and a carcinoma of the head of the pancreas obstructing the common bile duct was found. The patient died of a postoperative gastro-intestinal haemorrhage on May 30, 1950.

7. Mr. C. B., Winnipeg General Hospital No. 3455. An 80 year old white male patient admitted April 6, 1950 with symptoms of loss of weight, nausea, and vomiting for several weeks. He had previously been treated in hospital for a duodenal ulcer on several occasions. Examination revealed a wasted old man with moderate peripheral arterio-sclerosis, a palpable firm liver and early ascites. Investigation of his gastro-intestinal tract revealed a scarred duodenum. Shortly after

admission he became jaundiced, bile appeared in the urine, the serum bilirubin rose steadily and the alkaline phosphatase was elevated to 145 King units. It was believed that the etiology of the obstructive jaundice was carcinoma of the head of the pancreas or gall bladder. No surgical intervention was contemplated in view of the patient's age and general condition. Two estimations of serum antidiuretic activity were done; the first on May 23, 1950 at which time the serum bilirubin was 11.6 mgms. per cent, the cephalin flocculation ++, and the thymol turbidity 0.01; the second on June 21, 1950 at which time the serum bilirubin was 14.3 mgms. per cent, the flocculation tests were the same and the prothrombin time was 60 per cent of normal. The patient subsequently died on July 1, 1950 and at post mortem the liver was found to be moderately cirrhotic and a carcinoma of the gall bladder obstructing the common bile duct was also noted.

8. Mr. S. Y., Winnipeg General Hospital No. 34493. A 28 year old white male admitted June 11, 1950 with symptoms of jaundice and loss of appetite for three weeks. He was markedly icteric on admission and had obviously lost some weight. The liver was enlarged and the spleen was palpable but there were no other physical abnormalities. There was bile and an excess of urobilinogen in the urine. The serum bilirubin was 8.2 mgms. per cent, the alkaline phosphatase was 14 King units, the cephalin flocculation was +++, the thymol turbidity was 0.07, and the prothrombin time was normal. A serum antidiuretic level was estimated on June 14, 1950. A liver biopsy confirmed the diagnosis of

infectious hepatitis and the patient made an uneventful recovery.

9. Mr. H. M., Winnipeg General Hospital No. 34507. A 67 year old white male admitted June 12, 1950 with symptoms of chronic cough and expectoration for many years. On physical examination the patient was icteric and there was evidence of consolidation in the left lower lobe of the lung. The cardiovascular system was normal but the liver was enlarged, smooth, and firm. Subsequent investigation revealed a bronchogenic carcinoma of the left lung. Liver function tests also showed evidence of parenchymal liver disease which was diagnozed as portal cirrhosis. The serum bilirubin was 2.5 mgms. per cent. the alkaline phosphatase was 20 King units, the cephalin flocculation was +++, the thymol turbidity was 0.08, the prothrombin time was normal and the serum proteins were 1.3/4.6. There was no bile nor excess of urobilinogen in the urine. A serum antidiuretic estimation was carried out on June 14, 1950. The patient pursued a downhill course and died of bronchogenic carcinoma on July 10, 1950. A post mortem was not obtained.

CASE HISTORIES FOR SUBJECTS WITH MISCELLANEOUS DISEASES

1. Mrs. M. H., Winnipeg General Hospital No. 10613. A 54 year old female patient admitted to hospital on March 28, 1950 for investigation of weakness. In 1941 the patient was in a sanitorium with minimal pulmonary tuberculosis which has remained quiescent ever since. In October, 1948 she became weak and began to vomit, and was found to have

Addison's disease, presumably tuberculous in origin. She was treated with desoxycorticosterone pellets implanted in her back and responded well until just prior to admission. On this occasion her blood pressure was 90/50, she was weak and somewhat dehydrated and she showed an increase of cutaneous and gingival pigmentation. The water test and sodium estimations were normal. A serum antidiuretic level was determined on April 3, 1950. Following further desoxycorticosterone pellet implantation the patient's symptoms disappeared and the blood pressure rose to 125/80.

2. Mr. W. M., Winnipeg General Hospital No. 34024. A 21 year old white male admitted on May 25, 1950 with symptoms of epigastric pain, weakness and anorexia for two weeks. On physical examination there was increased pigmentation of the skin creases and of the buccal mucosa. The blood pressure was 60/30 and there were no other positive physical findings. A Thorn test and a Kepler water test were both positive. There was no evidence of tuberculosis and a mantoux test was negative. A good clinical response to desoxycorticosterone and salt was obtained and the diagnosis of idiopathic adrenal insufficiency was confirmed. A serum antidiuretic level was determined on June 6, 1950 before treatment was instituted.

3. Mr. A. U., Winnipeg General Hospital No. 15386. A 32 year old white male patient admitted to hospital on July 3, 1950 in mild Addisonian crisis. The patient was first diagnozed as idiopathic Addison's disease in March, 1947. Desoxycorticosterone pellets were

implanted in 1947 and again in April, 1949. The patient responded well to this therapy combined with added salt in the diet. On this occasion he was quite weak and appeared somewhat dehydrated, the blood pressure was 95/60 and cutaneous and gingival pigmentation were noted. He received 1,000 ml. of saline intravenously and the following morning a serum antidiuretic level was determined before hormone therapy was begun. A water test was positive, the serum sodium was 256 mgms. per cent and the 17-ketosteroid excretion was 3.5 mgms. in 24 hours.

4. Mr. F. Y., Winnipeg General Hospital No. 2095. A 62 year old white male patient admitted on March 14, 1950 with complaints of gross edema since 1947. He had previously been in hospital on many occasions. Investigation of his cardiovascular system was entirely normal as were his hepatic and gastro-intestinal systems. Previously because of marked albuminuria, and hypoproteinemia he had been diagnozed as a case of nephrosis. On this occasion he had bilateral pleural effusions, gross ascites and marked peripheral edema. The blood pressure was 120/75 and investigation of the heart was normal. There was no evidence of chronic intestinal insufficiency or liver disease. He continued to show marked albuminuria and his serum proteins were 1.9/2.7. A serum antidiuretic level was determined on March 23, 1950 before treatment was instituted.

5. Mr. H. L., Winnipeg General Hospital No. 34567. A 60 year old white male admitted on June 14, 1950 with symptoms of bilateral swelling of the legs for many years with a recent increase in edema.

Physical examination was entirely negative except for gross edema of both legs to the thighs. The edema was pitting to a slight degree and was somewhat painful. Investigation of the patient's cardiovascular, renal and hepatic systems was normal. It was decided that this was a case of lymphatic edema probably with a recent vascular thrombosis in the inferior cava to account for the sudden increase in edema. A serum antidiuretic level was determined on June 14, 1950.

6. Mr. P. P., Winnipeg General Hospital No. 19256. A 20 year old male patient who first noticed a lump in his neck in January, 1949. A biopsy showed the microscopic picture of Hodgkin's granuloma. He was followed in the Winnipeg General Hospital and received six courses of X-radiation and three courses of nitrogen mustard therapy. His course was fairly rapid and he quickly developed generalized lymphadenopathy, an enlarged liver and spleen, and a refractory anemia. He was admitted February 28, 1950 for further nitrogen mustard therapy. At this time he was wasted and there were enlarged lymph nodes in all node bearing areas; there was a small left pleural effusion, the liver and spleen were enlarged. The hemoglobin was 10.5 gm. per 100 ml. A serum antidiuretic level was estimated on April 21, 1950 before nitrogen mustard therapy was instituted.

7. Mr. C. S., Winnipeg General Hospital No. 2923. A 50 year old white male patient admitted to hospital on May 18, 1950 complaining of weakness and anorexia. He had previously been diagnozed as a case of chronic lymphatic leukemia in February, 1948 and had been receiving

X-radiation at intervals since that time. On this occasion he was very pale with a diffuse lymphadenopathy, but the liver and spleen were not enlarged. The hemoglobin was 5.1 gm. per 100 ml. and the white blood count was 94,000. He received several transfusions without any rise in hemoglobin value. The serum bilirubin was 1.3 mgms. per cent and it was felt that the patient was hemolyzing the red cells as quickly as he received them. His liver function was normal but the serum proteins were 2.8/0.9. A serum antidiuretic level was estimated on June 14, 1950, a week before the patient died. Post mortem revealed the changes of chronic lymphatic leukemia.